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THE NATIONAL ADVISORY EYE COUNCIL

vision research

A NATIONAL PLAN 1983-1987

1987 EVALUATION AND UPDATE

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U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

COMPLETED

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1987 EVALUATION AND UPDATE

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
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NIH Publication No. 87-2755

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Charles D. Phelps (1937—1985)

This volume is dedicated to Charles D. Phelps, M.D.,
who served as chairman of the Glaucoma Panel
for this *Evaluation and Update.*

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Foreword

In his Foreword to *Vision Research—A National Plan: 1983-1987*—the third in a series prepared under the auspices of the National Advisory Eye Council—NEI Director Carl Kupfer called this document "a major milestone in the history of the National Eye Institute. Never before have so many scientists representing such a broad and diverse range of disciplines, interests, and backgrounds participated in so comprehensive an effort to identify research needs and opportunities and establish priorities for the support of vision research."

Yet, Dr. Kupfer acknowledged, "despite its comprehensiveness and detail, this Plan will serve as only a guide to the Council and NEI staff over the next five years. The key determinant of what research the NEI will support will continue to be the proposals we receive for research grants whose quality is judged by the peers of the scientists who develop them. The National Plan is intended to augment, not supplant, the time-honored NIH peer review system."

Dr. Kupfer concluded his Foreword with the promise that "Over the next five years, the NEI will carefully monitor how closely the Institute's actual program development matches the recommendations of the Plan From this tracking we hope to identify areas in which additional measures may be required to stimulate needed research and possibly to find areas in which the Plan's recommendations should be modified."

The present report is a fulfillment of that pledge. It documents a thorough evaluation and update of the 1983-1987 National Plan—including a discussion of significant accomplishments since the Plan was published, an account of the status of ongoing NEI-supported research activity in terms of how well the Plan's recommendations have been fulfilled, and revised recommendations for the next two years. As background for this evaluation, readers are referred to the appropriate volumes of the 1983-1987 National Plan, which are cited at the end of the Introduction.

For convenience, the Plan's Resource Tables, which summarized the Plan's recommendations for each of the five NEI programs and presented target project levels for FY 1983, are included and updated through FY 1984, the base year for the evaluation. These are juxtaposed with revised tables that summarize the outcome of the evaluation, during which 44 percent of the Plan's 310 recommendations were either changed or deleted and over 60 new recommendations were added These tables indicate whether the updated recommendations are the same, new, or changed from those in the Plan and provide revised project target levels. Data on actual funding for FY 1985 and FY 1986 in these revised categories are included as well. These will be useful to the Council and its consultants and the NEI staff in preparing the next National Plan.

Stephen J. Ryan, M.D.
Chairman, National Advisory Eye Council
Program Planning Subcommittee

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Introduction

Eye diseases and blindness cost the Nation an estimated $16 billion per year. Over 11 million people are visually impaired and over 100 million wear eyeglasses or contact lenses. As our society and economy become more sophisticated and dependent on technology, the need for good vision becomes more and more acute, to ensure both an adequate quality of life and the ability to be a productive participant in the Nation's economic life. Perhaps for these reasons two Gallup Polls taken in the last decade showed blindness to be second only to cancer as the affliction most Americans fear.

It is the mission of the National Eye Institute to conduct and support basic and applied research directed toward the prevention and improved diagnosis and treatment of blinding and disabling eye diseases. As a means of discharging this mission in the most efficient and effective manner, the NEI has for over a decade engaged in formal, comprehensive program planning in conjunction with the National Advisory Eye Council.

In 1983, the National Advisory Eye Council published the third in a series of comprehensive national vision research plans. The National Eye Institute has used these documents to establish and implement program priorities and to guide both day-to-day decision making and long-range policy development. The National Eye Institute by design relies more than any other NIH component on investigator-initiated individual research to carry out its mission. (An estimated 85 percent of the 1987 NEI extramural research budget will fund individual investigator-initiated research grants. The comparable figure for NIH institutes that employ this support mechanism is 67 percent.) Therefore, the advice of representatives of the vision research community is considered particularly important in formulating these plans. This counsel helps assure that the Plans' goals, objectives, and recommendations are relevant to the current state of vision research and supply of research manpower and, hence, are achievable.

With each successive Plan, the NEI and the Council have attempted to build upon their experience with the preceding one to improve and refine their planning process. The most recent document, ***Vision Research: A National Plan—1983-87***, addresses every aspect of the NEI program, classifying each NEI-supported project as either a part of the Program Base—areas in which support should be continued at approximately current levels or, in selected cases, even reduced—or a Program Development Priority—an area judged to warrant greater emphasis and additional support—during the period covered by the Plan.

In FY 1985, midway in the period covered by this latest Plan, the Council decided to conduct a formal evaluation of its implementation and currentness by convening panels of experts aided by ad hoc consultants. Although the Council was satisfied that the Plan continued to reflect accurately most contemporary needs and opportunities in vision science, it wished to examine the current distribution and level of effort in those areas addressed by the Plan and to identify any important new research opportunities that had developed since the Plan was prepared. A further Council interest was to revise the Plan's text as required, particularly to make more specific or to consolidate the Plan's recommendations for the Program Base and Program Development Priorities in instances where there was ambiguity or redundancy.

The outcome of this evaluation has been an extensive update and revision of the Plan, based on both objective tracking data and the judgment of the scientific experts in each major field of vision research. For each subdivision of the NEI's five programs, the Evaluation contains an overview of the field of research, a discussion of recent progress in areas that were discussed in the Plan, highlights of new opportunities in developing areas of research, an analysis of the current balance of effort in the program (in terms of funding and scientific emphasis) subsequent to the Plan's publication, a discussion of the current relevance of the Plan's recommendations, and suggested changes in these recommendations based on the foregoing analysis.

History of NEI Program Planning

The legislation establishing the NEI authorizes it "to plan for research and training especially against the main causes of blindness and visual function." The need for ongoing planning involving a broad spectrum of scientific input is clear: developments in scientific concepts and technology have been so prolific that no one individual, no matter how well informed, can understand and appreciate them all, let alone know what research should be emphasized so that society will benefit maximally. Optimal distribution of research dollars, whether from the Federal Government, private industry, or philanthropy, is extremely difficult, but it is a goal worth striving toward to obtain maximal return on investment.

In 1973, therefore, in conjunction with its senior advisory body, the National Advisory Eye Council, the NEI embarked upon formal program planning. This modest initial effort has evolved into a major ongoing cooperative endeavor involving the NEI staff, the Council, and leading representatives of the vision research community.

1975-1979 Plan. In April 1975, the Council published *Vision Research Program Planning,* a two-volume publication covering the years 1976-1979. This document conveyed a philosophy of program planning that aims to balance the need to encourage scientific creativity with that to ensure accountability and fulfill the NEI's mission. This balance is achieved through a comprehensive, planning system that includes the formulation and implementation of specific program priorities and policies but continues to rely upon assessments of the scientific merit of individual grant applications (carried out through the traditional NIH peer review system) as the primary determinant of project funding. This 1975 report also identified 24 areas of special need and opportunity and provided the first systematic analysis and classification of the National Eye Institute's total program, including the presentation of detailed historical program data that could serve as a basis for future evaluation and planning.

1978-1982 Plan. Encouraged by the favorable response of the vision research community to this initial report, in 1977 the Council and NEI staff embarked upon a second, greatly expanded planning effort. For this project, the Council drew upon the advice of 150 experts who collectively represented most major fields of vision research and ophthalmology. They documented in detail the current state of eye research and engaged in a thorough exploration of the most likely paths for profitable research over the subsequent five years. Also, a survey of vision research support by other NIH components, other government agencies, and private sources was carried out. Based on this information, it was concluded that NEI then supported approximately 70% of vision research in the United States.

The result was a three-volume set, *Vision Research—A National Plan: 1978-1982,* published in April 1978. This document defined for the first time specific NEI program goals and objectives in each program and subprogram, described recent research and program accomplishments, outlined current research needs and opportunities, and identified several priorities in each of the five disease-oriented NEI programs.

1983-1987 Plan. The Council published its third report, the multivolume *Vision Research—A National Plan: 1983-1987,* in 1983. Much more comprehensive and detailed than the previous plans, this multivolume set—including a separately bound report on each of the five years. More than 350 scientists, representing all areas of vision research, helped refine and improve the NEI program planning system and provided scientific guidance for setting research priorities.

For each NEI program this Plan: describes the significant diseases and disorders encompassed by the program, including their public health impact; highlights the basic and clinical research disciplines and approaches that the program includes; redefines NEI program goals and objectives; surveys current support by the NEI and other organizations for relevant research (showing that NEI now supports 85% of vision research in the United States); reviews recent program and research accomplishments; describes current research needs, opportunities, and approaches; and makes specific recommendations concerning priorities for program development. In addition a number of cross-program scientific and administrative issues are dealt with as separate topics.

Program Base and Program Development Priorities.

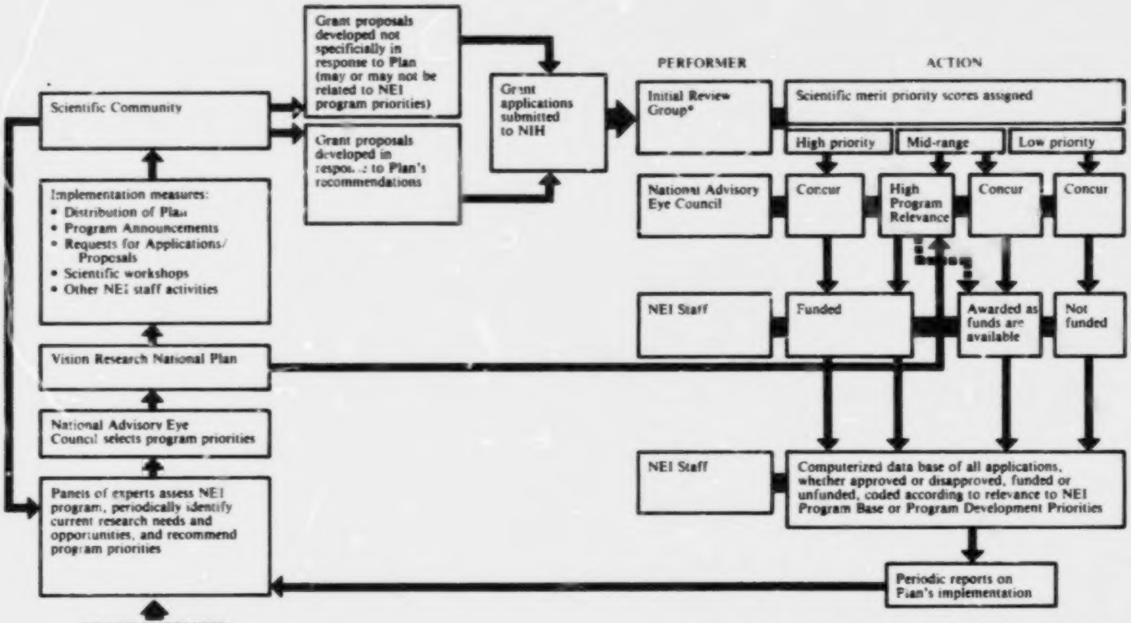
A significant innovation in the 1983-1987 National Plan (hereafter referred to as the Plan) was the presentation of program development recommendations in the context of a detailed classification and categorization of all ongoing research that the NEI supported. Those activities in each subprogram for which essentially level funding was projected over the next few years were grouped under the heading "Program Base", defined as:

> Areas of ongoing research where the current level of activity is considered adequate, or areas of ongoing research in which there may be great need for additional activity, but where, in the Panel's judgment, little or no opportunity (new methods or insights) exists at present to justify a significant expansion of effort.

Those research activities designated as Program Development Priorities were defined as:

> Areas of ongoing research in which new knowledge and techniques offer particular opportunities for scientific progress, or promising new areas of research in which there is little or no support at present but where there is both great need and high potential for success. Such areas are judged to warrant significantly increased support over the next five years, provided that high quality applications for research grants are forthcoming.

The National Eye Institute Program Planning System


Grant proposals developed not specificially in response to Plan (may or may not be related to NEI program priorities)
Scientific Community
Grant proposals developed in response to Plan's recommendations
Grant applications submitted to NIH
PERFORMER
ACTION
Initial Review Group*
Scientific merit priority scores assigned
High priority
Mid-range
Low priority
Implementation measures:
• Distribution of Plan
• Program Announcements
• Requests for Applications/ Proposals
• Scientific workshops
• Other NEI staff activities
National Advisory Eye Council
Concur
High Program Relevance
Concur
Concur
NEI Staff
Funded
Awarded as funds are available
Not funded
Vision Research National Plan
National Advisory Eye Council selects program priorities
NEI Staff
Computerized data base of all applications, whether approved or disapproved, funded or unfunded, coded according to relevance to NEI Program Base or Program Development Priorities
Panels of experts assess NEI program, periodically identify current research needs and opportunities, and recommend program priorities
Periodic reports on Plan's implementation
PROCESS STARTS HERE

* Study Sections of NIH Division of Research Grants or NEI Vision Research Program Committee.

Planning Principles

Although NEI's planning system has become increasingly detailed and comprehensive over the last fifteen years, several basic principles adopted in 1973 still provide direction to the Council and NEI staff. The most important of these are:

- The NIH investigator-initiated research project grant (R01) must be relied upon as the primary mechanism of NEI research support.
- The planning process must be prospective and continuous and its outcome should be communicated rapidly to the scientific community and the general public.

Implementation Guidelines

In addition, the NEI still abides by the following guidelines, also developed early in the NEI planning process, in implementing its national plans:

- Continue to fund first all proposals for research projects that are judged to be of the highest scientific quality by NIH study sections and other initial NIH peer review groups.
- Emphasize research that is most relevant to the prevention, diagnosis, and treatment of blinding and visually disabling disorders.
- Stress basic biological and applied clinical research on problems related to the most common causes of blindness and visual disability.
- When research involves laboratory animals, favor the utilization of species for which both scientific opportunity and technical feasibility permit the greatest amount of generalization to the human condition.

NEI Program Planning System

The figure "The National Eye Institute Program Planning System" represents schematically how the National Advisory Eye Council's national vision research plans interact with the traditional NIH peer review system that evaluates the scientific merit of grant applications. The diagram underscores the fact that the NEI and the Council, in response to the preceding guidelines, continue to rely primarily on the NIH peer review system for determining which grant applications will be approved and recommended for funding. The National Plan serves as an adjunct to the peer review process, first by encouraging the submission of grant applications for research in areas designated as Program Development Priorities, and second by providing additional input for Council and staff funding decisions.

Development, Dissemination, and Implementation of the Plan. The lower left corner of the diagram depicts

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the development of the Plan by the Council and the NEI in conjunction with leading representatives of the vision research community. Next, the published Plan is widely disseminated to scientists, and in selected instances specific measures are taken in to assist in its implementation. In general, however, the scientific community is relied upon to respond voluntarily to many of the Plan's recommendations; there is no earmarking of funds or extensive use of contracting to achieve these ends. Because leading representatives of the scientific community play a major role in the Plan's development, it is reasonable to expect such a response.

NIH Peer Review System. The upper left corner of the diagram depicts grant applications being submitted to NIH. Some of these applications are developed as direct responses to the Plan's recommendations, whereas others are not. In the latter case, many scientists will submit applications for research grants whose objectives may unintentionally coincide with the Plan's recommendations. Regardless, all grant applications are processed through the traditional NIH dual-level peer review system. The responsibilities of the initial review groups are to assess the scientific merit of an application and to judge the reasonableness of the budget proposed to carry out the project. The initial review group assigns a scientific merit (priority) score to approved applications; no score is assigned to disapproved applications. (Disapprovals are not shown on the diagram.)

The next level of review for those grant applications assigned to the National Eye Institute for funding consideration is the National Advisory Eye Council, which examines all applications whether approved or disapproved. Although the Council has the authority to return with comments an application to the initial review group for re-review, in practice it generally concurs with the initial review group's assessment. Virtually all the applications recommended by the Council for funding that receive the best scientific merit scores will be approved for payment by the NEI Director; those with the poorest scores will not. For the group of applications with midrange scores, some will be paid, some will not, depending on the availability of funds. Some applications that are not funded immediately may be held over to be paid later in the year. It must be emphasized that the primary—but not the only—factor that determines which applications are paid is the initial review group's scientific merit score.

Designation of High Program Relevance. For those applications with midrange scores, the margin between funded and unfunded may be only a few points. The Council does not have the authority to change scores, but it can recommend that a particular grant be given preferential consideration for payment. It does this by designating an application as having High Program Relevance, that is, having a high potential for fulfilling one of the Plan's Program Development Priorities. For example, such a proposal may concern an innovative approach to an important disease problem for which little or no current support exists. In any case, even though the Council may designate an application as having High Program Relevance, it is for the NEI Director, acting on advice of NEI program staff who also consider the potential effect on overall program balance of funding the application, to make the final decision on whether the grant is paid or not. The Director may or may not, at his discretion, fund any grant the Council recommends for approval, but he may not fund an application that has been disapproved.

All NIH Advisory Councils and Boards and institute staffs have the legal authority to make these funding recommendations and decisions. In carrying out their responsibilities in this regard, the National Advisory Eye Council and NEI staff have chosen to be guided by the Plan, which is based upon broad scientific input, supplemented by periodic data on its implementation. It is important to note that at any given Council meeting only an average three percent of all grant applications with midrange scientific merit scores are actually designated as having High Program Relevance. However, if future budget constraints warrant, the percentage of applications so designated may increase. The Council believes that judicious exercise of this option is vital and necessary to carry out the NEI mandate to improve the visual health of the American people.

NEI Program Structure

All vision research conducted and supported by the NEI is classified into five major programs encompassing a full spectrum of basic and applied research related to hundreds of eye and visual disorders that include the most important causes of visual deprivation and blindness in the United States. The five programs are: Retinal and Choroidal Diseases; Corneal Diseases; Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing. Because of the importance of visual impairment and its rehabilitation, including low vision, special consideration has been given in the National Plans to this broad topic, which has relevance to most of the diseases encompassed by the five NEI programs. Depending on the specific content of the proposed research and the availability of funds, research awards in this area may be funded in any of the five programs.

For purposes of program analysis, evaluation, and planning, each of the five programs is further divided into subprograms that generally focus on specific ocular and visual system diseases or disease processes, normal functioning, tissues, or systems. During each planning cycle, panels of scientific experts, working with the NEI staff and Council, have carefully examined the program structure used in the previous National Plan to judge its consistency with the current state of scientific knowledge and interest and to determine if that structure continues to provide a suitable framework for the the Council's program planning activities.

Among the five programs, there are naturally many areas of mutual and even overlapping concerns. For example, the ocular effects of diabetes are relevant to both the Retinal and Choroidal Diseases program and the Cataract program. Congenital and developmental eye disorders are common to all five programs. Because of these shared problems and concerns, progress in one area of vision research may well lead to advances in another. This indicates the need for improved communication among scientists in the various specialized fields of vision research and for their increased collaboration in investigations of mutual interest.

Evaluation and Update of The 1983-1987 National Plan

Midway through the period covered by the Plan, the Council and NEI staff decided to undertake an evaluation of its implementation through FY 1985 and to revise any sections that required updating. Although satisfied that the Plan continued to reflect accurately most of the major needs and opportunities in vision science, the Council and staff wanted to examine the current level and distribution of effort in those areas addressed by the Plan as well as recognize and encourage activity in important new areas that were just emerging at the time the Plan was prepared or which had developed subsequent to its publication. In particular, the rapid pace of advance in the fields of molecular biology, immunology, and neuroscience suggested many potentially fruitful applications in vision research; indeed, in some areas of these disciplines vision scientists had already achieved leadership status.

One impetus for evaluating the Plan was the availability for the first time of a database that afforded a practical means of assessing in detail and on a continuing basis the implementation of the Plan's recommendations. During the latter stages of the Plan's development the NEI established and perfected a computerized system for tracking grant applications wherein every NEI-supported project is coded according to its relevance to one of the Plan's recommendations. This resource can be used in analyzing past and current distributions of NEI grants according to their scientific objective and content In this way, comparisons can be made between what the Plan recommends and what has been actually funded, and new trends can be discerned. Such an assessment made midway in the planning cycle, it was believed, would indicate any need for altering the current Plan as well as help gain a headstart on preparing the next Plan.

These computerized analyses were first used to update the Plan's Resource Tables to show NEI's actual funding from FY 1981 (the base year of the 1983-87 Plan) through FY 1984 (the last complete year of funding when the evaluation began). The Council's Program Planning Subcommittee was reconstituted and, to assist them in evaluating and updating the Plan, five panels of experts—one panel for each of the five NEI programs—was established.

The Council charged the evaluation panels with the following tasks:

1. Review the Plan's recommendations in each subprogram or area of the five NEI programs.
2. Review the updated Resource Tables that show in detail actual NEI funding for the FY 1981-1984.
3. Ask the following questions:
   a. Do the Program Base and Program Development Priorities identified in the Plan adequately describe the full scope of current research in this field? Is there a compelling need to revise, add, or delete certain categories?
   b. Is there an appropriate balance of effort among and within subprograms, in terms of the Plan's stated program goals and objectives?
   c. Are the original project recommendations for FY 1983, as shown in the Plan's Resource Tables, still appropriate?
4. Update the Program Base and Program Development Priorities, giving a brief rationale for any changes.
5. Identify:
   a. Any major areas of the current Plan that should be revised.
   b. Any fast-developing areas of research that should be considered for increased support and be discussed in-depth in the next Plan.

Highlights of the Evaluation and Update

As the product of the panels' response to this charge, the present Evaluation goes far beyond the Council's and staff's original intent of merely fine-tuning the Plan. It is in fact a major revision of the Plan based on detailed assessments of recent NEI funding, reviews of recent research accomplishments, and forecasts of the potential impact of new research opportunities on NEI program development. The following are some highlights of each major section of the report:

Retinal and Choroidal Diseases. The themes of molecular genetics, immunology, and cell biology pervade the review of recent accomplishments and new and developing areas. The following recent recommendations are included:

- Put greater emphasis on molecular biological approaches to exploit recent developments in the search for factors that promote and inhibit abnormal proliferation of retinal blood vessels. It has been difficult to purify angiogenic factors, but this can now be done quite easily using heparin-affinity chromotography; therefore rapid progress can be expected in this area.
- Pursue studies of insulin receptors that have been discovered in the membrane of retinal vascular cells.
- Further investigate the metabolic pathway involved in the conversion of glucose to sugar alcohols through the action of aldose reductase and its relation to the development of diabetic retinopathy.
- Studies of the ocular tumor retinoblastoma have demonstrated a new class of oncogene, one where recessive mutations predispose to malignancy. Further molecular genetic studies of this tumor are needed.
- Integrate molecular biological and modern immunological methods to study the ocular immune response and inflammatory diseases of the eye, including seeking new therapeutic approaches based on these disciplines.
- In research on developmental and hereditary retinal degenerations, apply recombinant DNA probes to linkage studies of retinitis pigmentosa and related disorders to continue gaining new insights into the genetics of these diseases with the goal of isolating the defective genes.
- Emphasize basic research on the causes of macular degeneration, specifically to learn why this region of the retina is particularly susceptible during the aging process.
- Use recombinant DNA techniques to study gene expression and other aspects of normal retinal development.
- Continue using molecular genetic techniques to help unravel the basic machinery of visual excitation and phototransduction, the processes by which images are transformed into neural impulses that are transmitted to the brain.

Corneal Diseases. In making further progress against this group of disorders, there is particular need for increased support of ocular immunology, recently developed information on viral pathogenesis should be followed up, and investigations aimed at developing herpes vaccines should be strengthened. The report also makes the following recommendations:

- Investigate the use of recombinant DNA technology to elicit immunity against herpes simplex virus and to isolate the genes involved in the pathogenesis of this virus.
- Use simian varicella virus as an animal model for human varicella-zoster infection of the eye. New antiviral and anti-inflammatory agents should be developed for therapy of ocular infections due to adenoviruses and other viruses.
- Establish diagnostic techniques and evaluate medical therapy for amoebic keratitis and encourage new studies of onchocerciasis and leprosy.
- Solve the difficulties associated with studies of tear film and its abnormalities and try to remedy the paucity of effective therapeutic approaches to these problems.
- Develop new and innovative methods of drug delivery in ocular surface disorders.
- Collect data on the safety and efficacy of new keratorefractive surgical procedures in animals before they are applied to large numbers of patients.
- Study corneal endothelial cells in tissue culture to examine the effects of aging, surgery, and contact lens wear on normal structure and function.

Cataract. At present more than 70 percent of the cataract extractions in the U.S. are being done by the extracapsular method. This means that whole, intact lenses needed for cataract research are becoming quite scarce. One solution might be to arrange for obtaining intact lenses from such places as India, China, and South America, where intracapsular surgery still predominates.

Because of the success of some anticataractous agents developed through validated research, there has been a proliferation of substances purported to have anticataractous properties. Many of these substances have not been studied in the laboratory to verify their therapeutic values, yet they are being advanced by their manufacturers for use in clinical trials in the U.S., Europe, and Japan. This development is of increasing concern to the Council. The report also makes the following recommendations:

- Further investigate the molecular biology of lens development and differentiation, with particular emphasis on gene cloning and analysis of lens gene organization and regulation.
- Apply nuclear magnetic resonance imaging and other noninvasive techniques to the study of the lens.
- Develop cell culture systems to study lens cell division, gene transfer and expression, and drug effects on lens tissues.
- Initiate epidemiologic studies of cataract to determine environmental, nutritional, and genetic factors that may be involved in cataract development.
- Further explore the theory that the accumulated byproducts of oxidation in the lens due to lifelong exposure to sunlight is related to the onset of aging-related cataract.

Glaucoma. The report recommends that research included in the Aqueous Humor Dynamics—Inflow subprogram be de-emphasized and that in the Etiology, Epidemiology, Management, and Therapy subprogram and the Optic Nerve subprogram be given greater emphasis. There were suggestions to shift several categories of priorities, primarily from the Outflow and Optic Nerve subprograms into the Etiology, Epidemiology, Management, and Therapy subprogram. New priorities were also suggested in some areas. In addition, the report makes the following recommendations:

- Take advantage of new opportunities for glaucoma research in several developing areas, including immunogenetics, cell biology, and molecular biology, particularly for identifying the basic defect in the trabecular meshwork that underlies primary open-angle glaucoma and for determining how increased intraocular pressure damages the optic nervehead.
- In epidemiologic studies, emphasize efforts to determine which people are at risk for glaucoma and why people lose vision due to glaucoma. Studies of the value of treating ocular hypertension are stressed with emphasis particularly on initiating a clinical trial.
- Bring into glaucoma research experts from the fields of immunology and molecular biology to collaborate with research clinicians. Consideration should be given to holding workshops that would bring such basic scientists, as well as clinicians from other areas of medicine who are using these methods, into contact with clinical glaucoma researchers.

Strabismus, Amblyopia, and Visual Processing. The report makes the following recommendations:

- Shift the emphasis from identifying additional molecules involved in central visual processing to analyzing their functions and mechanisms of action.
- Emphasize the new opportunities for progress in understanding factors that facilitate regeneration and general guidance of optic nerve fibers.
- Increase emphasis on neural transplantation in mammals with the dual aims of eventually restoring lost visual function and, in the shorter term, learning more about the development of visual pathways in the brain.
- Use new imaging techniques, such as PET and NMR, to localize lesions and test the functioning of specific parts of the visual systems, especially in "higher order" visual processing.
- Expand the dialogue that has begun between basic and clinical scientists interested in amblyopia, so that animal models for this disorder can reflect the more subtle deficits in visual function often seen in the clinical situation. Also, encourage more active involvement of neuro-ophthalmologists in vision research.

Visual Impairment and Its Rehabilitation. Because the Subcommittee believed that the research priorities set forth in the Plan's special report on *Visual Impairment and Its Rehabilitation* were still highly relevant, it did not conduct a separate review of this area. The Subcommittee noted with pleasure the increases in the number of grants in this category, from 4 in FY 1981 to 13 in FY 1986, and recommended that an in-depth evaluation of progress and research needs in low vision and blindness be included in the next National Plan.

Updated and Revised Resource Tables

Two sets of tables (displaying, in turn, three levels of detail) are published face-to-face throughout this report. The set on the lefthand page, the "Updated National Plan Resource Tables," shows NEI funding data from FY 1981 through FY 1984. The set on the right, "Revised Resource Tables," shows the outcome of the Evaluation and Update of the Plan, provides funding data through FY 1986, and gives the recommended program development levels for achievement over the next two years.

This information is presented at three increasingly detailed levels: by program (at the end of this Introduction), by subprogram (at the beginning of each program panel report) and within each subprogram by Program Base or Program Development Priorities (following the text discussing each subprogram).

The projects tracked in these tables include the following award mechanisms: R01 (Project Grant—Traditional), R10 (Cooperative Clinical Research Grant), R23 (New Investigator Research Award), P50 (Specialized Clinical Research Center Grant), K04 (Research Career Development Award), K07 (Academic Investigator Award), and U01 (Cooperative Agreement). The number of R03 (Small Grant for Pilot Projects) and R43 and R44 (Small Business Innovation Research Grant, Phases I and II)—new NEI award mechanisms introduced after the Plan's publication—are shown in brackets.

Updated National Plan Tables. These tables compare actual NEI grant and funding data from FY 1981 through FY 1984 in the categories shown in the Plan's Resource Tables with what the Plan recommends for these categories by FY 1983. Occasionally, in addition to the Program Base and Program Development Priorities, a subprogram table will include a heading entitled "Additional Research Categories" (FY 1982 and later). This general designation was used in a few instances where an application or funded grant could not be classified in any of the Plan's categories. Also included are data on grant applications in each category for FY 1983 and 1984. The Panels used these tables in making their evaluation of the Plan and their recommendations for revisions.

Revised Resource Tables. The second set of tables similar in scope to the first, shows the outcome of the Panels' recommendations. These tables depict how the revised Program Base and Program Development Priorities compare with those in the 1983-1987 Plan (whether they are completely new, the same, or have been revised) and present grant data for FY 1984 through FY 1986 in these new categories. The second and third columns show the panels' recommendations for future awards in these categories—both for regular research projects and for clinical trials. These recommendations were based upon comparisons between FY 1984 data and what the Plan recommends for FY 1983 and upon the panels own judgement.

Although no discussion of funding in FY 1985 or FY 1986 is presented in this report, data for these years are presented here to serve as a bridge between the 1983-1987 Plan and the next plan, which will cover the years 1989-1990. In some cases it is apparent that the Update Panel's recommended number of projects were already met or exceeded by FY 1986. In other cases where the Update Panels recommendations significantly exceeded the FY 1986 level, particularly in the Program Base, this is usually because the Panels have reaffirmed the Plan's original recommended level for FY 1983 but actual funding decreased in the interim. Data for the years 1985-87 will be analyzed in the next plan.

It is important to note that the number of projects shown in any given line of the FY 1984 column of the Updated Tables may differ from that for a comparable entry in the FY 1984 column in the Revised Tables. Such differences occur not only within, but among subprograms. This is because all the FY 1984 grants included in the the Updated Tables were, for the Revised Tables, reanalyzed and recoded according to their relevance to the revised recommendations. Comparisons between the FY 1984 columns in the two tables reflect the changes made by the *Evaluation and Update* in the detailed NEI program structure.

Originally, the 1984 projects were coded piecemeal as their applications were received and logged into NEI's tracking system. The evaluation panels, however, examined each funded grant as part of the total portfolio within each program. It is not surprising therefore that in several instances, even when the categories did not change substantially between Plan and the Update, panel members and NEI staff found it advisable to reassign individual grants to different categories, even shifting them to different subprograms if that seemed appropriate. For the sake of historical continuity, the text of the report accounts for this reordering in some detail, particularly in instances where information in the tables alone does not specifically account for it.

Interpretation of Tracking Data

In reviewing the data comparing actual NEI funding in the years following the Plan's publication with what the Plan recommends, it is important not to over-interpret either agreement or difference between the two—especially between the recommended project levels and the actual funding within and among subprograms. In particular, due to budgetary constraints, the total number of NEI grants awarded in FY 1983, 990 plus 43 in "new mechanisms," fell short of the total of 1322 that the Plan recommends for that year. Thus, it was inevitable that the Plan's recommended project goals for most Program Development Priorities in the subprograms would not have been achieved by that year. However, in a number of cases such goals were met by FY 1984, the base year of this *Evaluation and Update*, and in a few instances were even exceeded a remarkable accomplishment given the overall funding levels for that year. On the other hand, a number of Program Base categories also exceeded their recommended funding levels by FY 1984—something that might be considered undesirable, especially if such funding occurred at the expense of growth in the Program Development Priorities.

Any number of explanations and interpretations are possible for such variations between recommended and actual levels and therefore each case must be evaluated separately, but the primary reason is that, as noted above, the NEI and the Council continue to rely primarily on peer-reviewed, individual investigator-initiated research projects to fulfill NEI's mission. Projects that receive the most favorable review by NIH scientific peer review groups will almost surely be funded whether they coincide with the Plan's recommendations or not. Hence, high-quality applications in Program Base categories are still likely to be funded, whereas applications for research in Program Development Priorities that are judged of a lower quality are not likely to be funded.

Other explanations are rooted in the inherent constraints and imperfections of any planning system for biomedical research, limitations that the NEI and Council readily acknowledge. A field of research that appeared to be promising when the Plan was prepared may have not borne out the high expectations of those who recommended that it be designated a priority. In other areas, a major discovery may suddenly have opened new opportunities that were not anticipated by the Plan and which several investigators were quick to exploit. In still other areas, the need and the opportunity for additional research may still be there; but some catalyst, such as a special solicitation for grant applications or a workshop, is needed to spark activity.

The tracking data can therefore only suggest areas in which more probing analyses of funding trends may be worthwhile. They characterize in a general way the current mix of research supported by the NEI and may reveal the need to revise program priorities (see the revisions contained in this report) or the need to take further implementation measures, such as those outlined in Volume One of the Plan, to try to fulfill the Plan's original recommendations.

Update Panel Recommendations

Research Grants. In the Revised Resource Tables, the number of grants recommended by the Panels to be awarded over the next two years is the sum of their estimate of new and continuing awards that could be made, given both the needs and opportunities in the field, tempered by forecasts of the likely level of future funding. The actual number of grants that will be supported in these areas will most likely be either more or less than these projections, depending on the quality, quantity, type, and kind of applications the NEI receives and the availability of funds. In making these estimates the Panels took into account the following factors for each category of research considered:

- Degree of relevance to the program's goals and objectives;
- Current level of NEI support;
- Recent research accomplishments;
- Availability of trained manpower; and
- Likelihood of significant progress over the next two to three years.

Clinical Trials. The numbers of projects recommended for clinical trials are listed in the Revised Tables separately from those for other research. This has two major advantages. First, it serves to highlight for the research community, as well as for those who review and approve the NEI's budget at various governmental levels, those areas in which continuing or new clinical trials have been judged to offer great potential benefit to the public. Second, by accounting separately for clinical trials—whose multiple components often have an average per unit cost significantly less than that of an average research project grant—a more balanced and realistic projection of total program needs and priorities can be provided. The numbers of projects shown for recommended clinical trials have been adjusted to incorporate trials that are known to be under development and which are likely to be funded within the next two years.

In some categories it is apparent that FY 1986 funding has already exceeded the funding targets of the new Panels that were set. These data will be carefully reviewed by the Council and its consultants in preparing the next National Plan.

Evaluation and Update Structure

In the following pages each section of the Plan is reviewed and analyzed by subprogram according to the following format:

Perspective on Recent Research. This is a brief general introductory section discussing broadly any changes that have occurred in this field of research since the 1983-1987 National Plan was published. This includes an overview of (1) recent developments in areas discussed in the Plan and (2) exciting new areas that have opened up since the Plan was published. These changes are discussed in more detail in the next two sections.

Progress in Areas Discussed in the 1983-1987 Plan. This section updates specific portions of the Plan. It includes further elaboration of the areas of research highlighted in the preceding section with particular emphasis on significant recent research accomplishments.

New and Developing Areas of Research. This section discusses either existing areas of science in which major new opportunities have developed since the Plan was prepared or revolutionary new methods and techniques that were unforseen at that time. The specific opportunities for applying these new methodologies to research in this subprogram are discussed.

Balance of Effort Within Subprogram. This section includes a discussion of NEI funding of research in the subprogram since the Plan was published. Questions addressed by the panels included:

- Has funding remained essentially stable, declined, or increased and what shifts have occurred, particularly vis-à-vis the Program Base and Program Development Priorities categories?
- Have any grants already been funded in the new and developing areas discussed in the preceding section?
- Has any relevant research in this area been supported by other government agencies, private industry, or private foundations?

Adequacy and Current Relevance of the Program Base and Program Development Priorities. This section presents an evaluation, in the context of the discussions in the proceeding sections, of both the appropriateness of the Plan's recommendations in this subprogram and the expected number of projects that were recommended in the Plan for FY 1983. The following are some examples of questions that were asked and addressed:

- Should some Program Base categories become Program Development Priorities, or vice versa, and why?

- For instance, have new knowledge and techniques made it feasible to expand research in areas for which great need has existed but for which few opportunities for productive research have heretofore existed?
- Or, have some Priorities reached an optimal funding level in the context of the overall budget and should now be considered part of the Base?
- Or, did the great potential shown in some Priorities simply not live up to expectations?
- Are some of the Plan's recommendations too specific or too general?
- Are the Plan's project funding recommendations in certain (or all) areas overly optimistic or, conversely, did some areas grow more than the Plan recommended. If the latter, is this because certain opportunities were underestimated and/or unforeseen, or was it simply because a large number of high-quality grant applications were received in these areas?
- Were grant applications received in a Priority in which little actual funding had occurred but were not funded because of their relatively poorer priority scores?
- Should some Priorities in which little activity has yet occurred continue to be emphasized nonetheless because of their great importance to the field, and is there anything the NEI or others can do to stimulate activity in such areas?

Recommended Changes in Program Base and/or Progress Development Priorities. Based upon the foregoing evaluation, this section discusses the changes recommended, if any, in the Plan's Program Base and Program Development Priorities, and the rationale for such changes.

Updated and Revised Resource Tables. These update the Plan's Resource Tables and provide an estimate of the number of projects that optimally could be funded in each Program Base and Program Development Priority category over the next two years, keeping in mind the program needs, scientific opportunity, and existence of an adequate manpower base to do the work.

Vision Research—A National Plan: 1983-1987.

For further reference, readers of this *Evaluation and Update* are referred to the following volumes and sections of the Plan:

Executive Summary (Overview of the entire Plan).
Volume One—The 1983 Report of the National Advisory Eye Council (Background, Summary Panel Reports and Resource Requirements, Implementation Strategy, Cross-Cutting Research Areas and Issues, Planning Participants, Planning Strategy and Process).

Volume Two—Reports of the Program Panels

- **Part One**—*Report of the Retinal and Choroidal Diseases Panel*
- **Part Two**—*Report of the Corneal Diseases Panel*
- **Part Three**—*Report of the Cataract Panel*
- **Part Four**—*Report of the Glaucoma Panel*
- **Part Five**—*Report of the Strabismus, Amblyopia, and Visual Processing Panel*
- **Part Six**—*Report of the Panel on Visual Impairment and Its Rehabilitation.*

Volume Three—Support for Vision Research (Data on vision research projects supported by the NEI in FY 1981 and by other government and private organizations in 1980).

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UPDATED NATIONAL PLAN RESOURCE TABLE

Figures shown below are
Number of Projects* [New Mechanisms]
Dollars in Thousands

		Plan Rec.				Applications FY 1983-84		
Program	FY 1981	FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
Retinal and Choroidal Diseases	381	492	386[21]	390[14]	384[12]	595	235	39.5
	33,535	51,660	36,064	41,157	45,807			
Corneal Diseases	162	215	163[15]	151[10]	152[12]	245	101	41.2
	15,849	23,005	17,354	18,435	19,895			
Cataract	101	137	102 [6]	94 [6]	103 [4]	161	66	41.0
	8,970	14,796	9,938	10,602	11,426			
Glaucoma	90	125	88 [4]	98 [5]	97 [3]	130	53	40.8
	8,780	14,500	9,659	11,306	12,716			
Strabismus, Amblyopia, and Visual Processing	268	353	244[12]	257 [8]	266[11]	448	174	38.8
	22,070	34,594	21,351	24,972	27,538			
TOTAL	1002	1322	983[58]	990[43]	1002[42]	1579	629	39.8
	89,204	138,555	94,366	106,472	117,382			

*Includes current clinical trial awards.

REVISED RESOURCE TABLE

Figures shown below are
Number of Projects* [No. R03, R43, R44]
Dollars in Thousands

	Projects FY 1984 [No. R03, R43, R44]	*Update* Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
		Research Grants	Clinical Trials		
Retinal and Choroidal Diseases	383 [12] 45,714	527	103	438 [10] 55,558	468 [11] 60,741
Corneal Diseases	154 [12] 19,892	216	20	166 [13] 24,038	172 [13] 24,863
Cataract	104 [4] 11,515	110	14	104 [7] 13,044	111 [8] 12,989
Glaucoma	97 [3] 12,718	129	31	98 [2] 13,553	99 [7] 14,166
Strabismus, Amblyopia, and Visual Processing	267 [11] 27,547	351	28	265 [11] 28,645	267 [5] 29,708
TOTAL	1005 [42] 117,386	1333	196	1071 [43] 134,838	1117 [44] 142,467

*Includes current clinical trial awards.

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RETINAL AND CHOROIDAL DISEASES

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UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

Figures shown below are
Number of Projects [New Mechanisms]
(Percent of Projects in Program)
Dollars in Thousands

	FY 1981	Panel Rec. FY 1983	FY 1982	FY 1983	FY 1984	Applications FY 1983-84 Received	Funded	Percent
Vascular, Inflammatory, and Neoplastic Disorders of the Retina and Choroid (1-E1)								
1. Diabetic Retinopathy, Sickle Cell Retinopathy, and Other Vascular Abnormalities (1-E2)	51 (13.4) 5,127	60 (12.2) 6,300	53 [0] (13.7) 5,473	50 [6] (12.8) [illegible] 898	47 [2] (12.2) 6,079	93	34	36.6
2. Inflammatory Disorders (1-E3)	14 (3.7) 1,558	25 (5.1) 2,625	15 [1] (3.9) 1,403	15 [0] (3.8) 1,480	13 [0] (3.4) 1,36[illegible]	21	7	33.3
3. Tumors (1-E4)	18 (4.7) 1,887	29 (5.9) 3,045	20 [1] (5.2) 2,000	20 [1] (5.1) 2,066	17 [1] (4.4) 2,209	33	11	33.3
Degenerative Disorders of of the Retina (1-F1)								
4. Developmental and Hereditary Disorders (1-F2)	42 (11.0) 3,[illegible]09	59 (12.0) 6,195	41 [2] (10.6) 4,253	39 [2] (10.0) 4,675	33 [0] (8.6) 5,140	58	19	32.8
5. Macular Degeneration (1-F3)	18 (4.7) 1,418	34 (6.9) 3,570	19 [1] (4.9) 1,396	22 [0] (5.6) 2,245	22 [7] (5.7) 2,613	18	8	44.4
6. Retinal Detachment and Vitreous Disorders (1-F4)	18 (4.7) 1,722	27 (5.5) 2,835	17 [3] (4.4) 1,867	16 [0] (4.1) 1,838	18 [0] (4.7) 2,660	24	11	45.8
7. Toxic and Environmental Disorders (1-F5)	2 (0.5) 91	4 (0.8) 420	2 [1] (0.5) 136	2 [0] (0.5) 126	2 [1] (0.5) 151	6	2	33.3
Fundamental Processes and Retinal Disorders (1-G1)								
8. Retinal Pigment Epithelium (1-G2)	24 (6.3) 1,931	37 (7.5) 3,885	21 [0] (5.4) 1,824	26 [0] (6.7) 2,694	27 [2] (7.0) 3,469	32	17	53.1
9. Photoreceptors, Visual Pigments, and Phototransduction (1-G3)	112 (29.4) 9,514	112 (22.8) 11,760	122 [5] (31.6) 11,135	120 [4] (30.8) 12,363	112 [2] (29.2) 12,666	151	62	41.1

UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

		Panel Rec.	Figures shown below are Number of Projects [New Mechanisms] (Percent of Projects in Program) Dollars in Thousands			Applications FY 1983-84		
	FY 1981	FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
10. Retinal Organization, Neurotransmission, and Adaptation (1-G4)	64 (16.8) 4,729	71 (14.4) 7,455	62 [6] (16.1) 5,403	69 [0] (17.7) 6,813	81 [1] (21.1) 8,285	124	54	43.5
11. Glial Cells and the Retinal Microenvironment (1-H1)	6 (1.6) 437	9 (1.8) 945	6 [0] (1.6) 350	5 [0] (1.3) 309	4 [0] (1.0) 258	3	1	33.3
12. Rescue and Regeneration of Neurons in the Optic Nerve and Retina (1-H2)	2 (0.5) 136	7 (1.4) 735	1 [0] (0.3) 106	3 [1] (0.8) 233	4 [0] (1.0) 356	9	5	55.5
Related Areas of Research Opportunity and Need								
13. Noninvasive Techniques in the Study of Retinal Disorders (1-K1)	10 (2.6) 1,176	18 (3.7) 1,890	7 [1] (1.8) 718	3 [0] (0.8) 417	4 [1] (1.0) 556	23	4	17.4
14. Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models (1-L1)	0 (0.0) 0	0 (0.0) 0	0 [0] (0.0) 0	0 [0] (0.0) 0	0 [0] (0.0) 0	0	0	0.0
PROGRAM TOTAL	381 (100.0) 33,535	492 (100.0) 51,660	386 [21] (100.0) 36,064	390 [14] (100.0) 41,157	384 [12] (100.0) 45,807	595	235	39.5

REVISED PROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
		Research Grants	Clinical Trials		
Vascular, Inflammatory, and Neoplastic Disorders of the Retina and Choroid (1-E1)					
1. Diabetic Retinopathy, Sickle Cell Retinopathy, and Other Vascular Abnormalities (1-E2)	48 [2] (12.5) 6,248	61 (11.6)	45 (43.7)	74 [1] (16.9) 9,248	73 [2] (15.6) 9,785
2. Inflammatory Disorders (1-E3)	14 [0] (3.7) 1,423	24 (4.6)	8 (7.8)	13 [1] (3.0) 1,452	15 [1] (3.2) 1,767
3. Tumors (1-E4)	17 [1] (4.4) 2,207	28 (5.3)	30 (29.1)	39 [2] (8.9) 4,488	42 [0] (9.0) 4,838
Degenerative Disorders of of the Retina (1-F1)					
4. Developmental and Hereditary Disorders (1-F2)	36 [0] (9.4) 5,509	70 (13.3)	3 (2.9)	37 [2] (8.4) 6,134	47 [1] (10.0) 7,675
5. Macular Degeneration (1-F3)	23 [2] (6.0) 2,666	25 (4.7)	15 (14.6)	31 [0] (7.1) 3,327	28 [0] (6.0) 3,618
6. Retinal Detachment and Vitreous Disorders (1-F4)	18 [0] (4.7) 2,739	31 (5.9)	2 (1.9)	14 [1] (3.2) 2,708	19 [2] (4.1) 3,444
7. Toxic and Environmental Disorders (1-F5)	2 [1] (0.5) 151	5 (0.9)	0 (0.0)	2 [0] (.5) 233	2 [0] (.4) 223
Fundamental Processes and Retinal Disorders (1-G1)					
8. Retinal Pigment Epithelium (1-G2)	27 [2] (7.0) 3,536	45 (8.5)	0 (0.0)	33 [0] (7.5) 4,756	32 [0] (6.8) 4,489

REVISED PROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
		Research Grants	Clinical Trials		
9. Photoreceptors, Visual Pigments, and Phototransduction (1-G3)	107 [2] (27.9) 12,130	120 (22.3)	0 (0.0)	105 [0] (24.0) 13,234	108 [2] (23.1) 13,486
10. Retinal Organization, Neurotransmission, and Adaptation (1-G4)	81 [1] (21.1) 8,225	88 (16.7)	0 (0.0)	79 [3] (18.0) 8,703	89 [2] (19.0) 9,523
11. Glial Cells and the Retinal Microenvironment (1-H1)	4 [0] (1.0) 258	12 (2.3)	0 (0.0)	4 [0] (.9) 347	4 [0] (.9) 345
12. Rescue and Regeneration of Neurons in the Optic Nerve and Retina (1-H2)	4 [0] (1.0) 356	8 (1.5)	0 (0.0)	4 [0] (.9) 361	4 [1] (.9) 532
Related Areas of Research Opportunity and Need					
13. Noninvasive Techniques in the Study of Retinal Disorders (1-K1)	2 [1] (0.5) 356	10 (1.9)	0 (0.0)	3 [0] (.7) 567	5 [0] (1.1) 1,016
14. Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models (1-L1)	0 [0] (0.0) 0	0 (0.0)	0 (0.0)	0 [0] (.0) 0	0 [0] (.0) 0
PROGRAM TOTAL	383 [12] (100.0) 45,714	527 (100.0)	103 (100.0)	438 [10] (100.0) 55,558	468 [11] (100.0) 60,741

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VASCULAR, INFLAMMATORY, AND NEOPLASTIC DISORDERS OF THE RETINA AND CHOROID

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Diabetic Retinopathy, Sickle Cell Retinopathy, and Other Vascular Abnormalities

1

Perspective on Recent Research

Research on the vascular retinopathies continues to grow at a rapid rate with major emphasis on diabetic retinopathy because of the large number of people at risk for this disease. Ninety percent of patients with insulin dependent diabetes mellitus will have some degree of retinopathy after 15 years; after 30 years, 50 percent will have proliferative disease. Animal models remain important, but thus far the dog seems the only one manifesting retinopathy typical of that seen in man. The accumulation of sorbitol, triggered by the enzyme aldose reductase (AR), has been hypothesized to be responsible for the degeneration of intramural pericytes in retinal blood vessels in diabetic retinopathy. A clinical trial is underway to test the effect of an aldose reductase inhibitor, sorbinil, on the progression of diabetic retinopathy.

The ability to culture retinal vascular cells has led to the discovery of membrane insulin receptors and possible cell dependencies. Growth hormone may also play a role in the development of diabetic retinopathy and small prospective studies of various hormone relationships are underway. Recent studies suggest that prognostic information may be available from psychophysical and electrophysiological analyses of the visual system. Finally, clinical trials continue to be valuable in testing the effectiveness of various techniques of photocoagulation. Panretinal photocoagulation has been shown effective in proliferative retinopathy and, more recently, focal treatment of microaneurysms has been demonstrated helpful in patients with diabetic macular edema. Photocoagulation has been advocated for sickle cell retinopathy, and cryocoagulation is being tested for the retinopathy of prematurity. Blood flow and fluorescein dye leakage measurements remain important methods for the study of ocular vascular abnormalities. New methods, including laser doppler and laser scanning, may provide new diagnostic and prognostic information. It is clear, however, that even more concentrated research is needed to find better methods for the treatment and, ultimately the prevention of ocular vascular diseases.

Progress in Areas Discussed in the 1983-1987 Plan

Tissue culture of retinal capillary cells is of great value in the study of retinal vascular diseases because it has now become possible to culture both pericytes and endothelial cells. Retinal pericytes in culture are unusually sensitive to insulin; the hormone can stimulate both metabolic and growth effects at physiological concentrations.[1] Several laboratories are now characterizing the insulin receptors on retinal capillary cells and the receptors for and effects of other growth factors. Microperfusion of isolated retinal vessels may provide new opportunities for study of the blood-retinal barrier.[2] The search for angiogenesis factors has continued to provide useful new information. A retina-derived factor, active in angiogenesis assays, has been isolated and partially characterized.[3,4] To evaluate the possible role of such factors in retinopathy, however, it has become increasingly important to understand the actual cellular and biochemical events involved in new blood vessel formation.

Laser doppler velocimetry has been used to detect alterations in retinal blood flow in patients with diabetic retinopathy.[5,6] Using this technique, investigators have discovered that retinal blood flow is reduced by retinal photocoagulation.[6,7]

New developments have served to re-emphasize the importance of animal models of diabetic retinopathy. It has been known that diabetic dogs eventually develop lesions that resemble those of human nonproliferative diabetic retinopathy.[8] Experimental galactosemia has recently been found to result in the development of retinal lesions that are identical to those in the diabetic dog.[9] This new model provides an opportunity to study a range of retinopathic alterations in the absence of many of the general metabolic consequences of diabetes. Some, but not all, of these extensive retinal alterations are produced in the galactosemic rat model. Independent laboratories have recently demonstrated that the retinal capillary basement membrane thickening that does develop in these animals can be completely prevented by the administration of sorbinil, an aldose reductase inhibitor.[10,11] This has added new impetus to studies of the possible role of this enzyme as a factor in the development of diabetic retinopathy.

The Branch Vein Occlusion Study (BVOS) has been completed.[12,13] The results demonstrate that argon laser photocoagulation improves the visual outcome to a significant degree in eyes with branch vein occlusion and visual acuity reduced from macular edema to 20/40 or worse.

A randomized, prospective, multicenter clinical trial has begun to assess the safety and efficacy of cryotherapy of the peripheral retina to prevent the progression of acute retinopathy of prematurity. [The study includes 23 participating clinics and 3 central units.]

New and Developing Areas of Research

The discovery that the vascular endothelial cell growth factors bind to heparin is an important breakthrough.[14] Heparin or heparin-like molecules may play an important role in mediating the effects of these factors.[15] Purification of angiogenic factors has been difficult, but with the introduction of heparin-affinity chromatography, rapid progress can now be expected in this area.[16] New developments in the search for inhibitors of angiogenesis add even further impetus.[17] The metabolism of isolated retinal vascular cells, including studies of insulin receptors and the susceptibility of these cells to growth factors should be emphasized further. The possible role of the polyol pathway in the development of diabetic retinopathy needs further investigation. An increased utilization of the galactose dog model seems important since the pathology occurs without concomitant generalized insulin effects.

Balance of Effort Within Subprogram

In FY 1984 a total of 47 research project grants were funded in this subprogram, excluding one small grant and one small business innovation research (SBIR) grant. There were also 17 contract-supported clinical centers for the Diabetic Retinopathy Vitrectomy Study, 23 clinical centers for the Early Treatment Diabetic Retinopathy Study, and 5 additional centers for ancillary functions for these clinical trials.

The Plan recommends that there be an increase in the number of grants funded in this subprogram but from 1981 to 1984 the actual number of grants decreased from 51 to 47 grants. This occurred during a time when the total number of all Retinal and Choroidal Diseases grants funded remained essentially unchanged.

The major area of difficulty in this subprogram in terms of funding is the study of the location of, and mechanisms responsible for, the breakdown of the blood-retinal barrier in retinal vascular disease (B2). The Plan recommended that the number of projects funded in FY 1981 in this category be maintained, but they actually decreased from 13 in FY 1981 to only 8 in FY 1984, even though 50 percent of the applications received by the NEI in this category were funded.

In general, the diversity of activity underway in the subprogram is appropriate and the quality of research is high. However, more should be done in all of the categories.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Program Base consists of 5 categories of grant-supported research which were projected for level funding from FY 1981 to FY 1983. These are: characterization of the factors responsible for the growth of new retinal blood vessels; study of the location of and mechanisms responsible for the breakdown of the blood-retinal barrier in early diabetes, hypertension, other retinal vascular diseases; clinical trials of treatment for retinal vascular diseases; epidemiological studies on various types of retinal vascular diseases; and development of methods for diagnosing and treating retinal-vascular disorders.

The Program Development Priorities are to expand studies of the metabolism of retinal vascular cells, to develop new animal models of vasoproliferative retinopathies, investigate approaches that will prolong retinal survival time after vascular occlusions, improve noninvasive methods of all types, and to encourage basic research that would lead to pharmacological management of retinal vascular disorders.

In this last Program Development Priority (D5), there were no grants in 1981. The Plan recommends that 2 be funded by FY 1983. However, in FY 1984 there still were no grants in this area, although 2 small grants of one-year duration were funded in FY 1983. Even though there were only 6 applications received for research grants in this area, the Evaluation Panel recommends retaining this Priority because it is extremely important to develop a medical means of handling retinal vascular disorders, such as sorbinil and aspirin which are currently being tested in clinical trials. In addition, there may be other therapeutic approaches such as the use of artificial (e.g., perfluorocarbon) blood exchange.

Recommended Changes in Program Base and/or Program Development Priorities

The Evaluation Panel does not recommend major changes in the Program Base or the Program Development Priorities in this subprogram and is, in general, satisfied with the current areas of emphasis. A greater emphasis on molecular biologic approaches is needed, however, to exploit effectively recent developments in the search for angiogenesis factors and inhibitors and in the study of the metabolism of retinal vascular cells.

Further research aimed at the development of more effective treatment of retinal vascular occlusions is also necessary. Finally, epidemiological studies on the incidence and prevalence of retinal vascular diseases are considered of great importance.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF RETINA/CHOROID: DIABETIC/SICKLE CELL RETINOPATHY & OTHER VASC. ABNORMAL. (1-E2)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Characterize factors responsible for the growth of new retinal blood vessels. (B1)	3	3	6	4	4	8	1	12.5
2. Study the location of and mechanisms responsible for the breakdown of the blood-retinal barrier in retinal vascular diseases. (B2)	13	12	8	8 [2]	8	14	7	50.0
3. Continue to support clinical trials of treatments for retinal vascular diseases and test the efficacy of rigorous blood sugar control in the prevention of diabetic retinopathy. (B3)	10	10	10	9	8	2	0	
4. Encourage epidemiologic studies on various types of retinal vascular disease. (B4)	4	4	4	3	4	5	2	40.0
5. Improve methods for diagnosing and treating retinal vascular disorders. (B5)	7	8	8	7 [2]	6 [1]	18	8	44.4
TOTAL FOR PROGRAM BASE	37	37	36 [0]	31 [4]	30 [1]	47	18	38.3
PROGRAM DEVELOPMENT PRIORITIES								
1. Expand studies of the metabolism of retinal vascular cells using isolated specimens and cells grown in tissue culture. (D1)	7	9	7	9	9 [1]	28	10	35.7
2. Develop new animal models of vasoproliferative retinopathies. (D2)	6	7	8	7	5	10	3	30.0
3. Investigate approaches that prolong retinal survival time after major vascular occlusion and permit restoration of retinal function. Investigate methods for revascularizing areas of ischemic retina. (D3)	0	2	0	0	2	1	0	
4. Improve noninvasive methods for determining oxygen saturation in retinal blood vessels. (D4)	1	3	2	3	1	1	1	100.0

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF RETINA/CHOROID: DIABETIC/SICKLE CELL RETINOPATHY & OTHER VASC. ABNORMAL (1-E2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
5. Encourage basic research which will lead to the pharmacological management of retinal vascular disorders. (D5)	0	2	0	0 [2]	0	6	2	33.3
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	14	23	17 [0]	19 [2]	17 [1]	46	16	34.8
TOTAL FOR SUBPROGRAM	51	60	53 [0]	50 [6]	47 [2]	93	34	36.6
(% OF PROGRAM)	(13.3)	(12.1)	(13.7)	(12.8)	(12.2)			

REVISED SUBPROGRAM SUMMARY RESOURCE TABLE.

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF RETINA/CHOROID: DIABETIC/SICKLE CELL RETINOPATHY & OTHER VASC. ABNORMAL. (1-E2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Study the location of and mechanisms responsible for the breakdown of the blood-retinal barrier in retinal vascular diseases. (B1)	SAME (WAS B2)	5	11	0	5	9
2. Encourage epidemiologic studies on various types of retinal vascular disease. (B2)	SAME (WAS B4)	6	5	0	5	5
3. Improve methods for diagnosing and treating retinal vascular disorders. (B3)	SAME (WAS B5)	9 [1]	9	0	9	6 [1]
TOTAL FOR PROGRAM BASE		20 [1]	25	0	19 [0]	20 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Continue to support clinical trials of treatments for retinal vascular diseases and test the efficacy of rigorous blood sugar control in the prevention of diabetic retinopathy. (D1)	MOVED (WAS B3)	8	0	45	36	28
2. Isolate and characterize retinal angiogenic factors and inhibitors. (D2)	NEW (INCLUDES OLD B1)	3	7	0	6	7
3. Expand studies of the metabolism of retinal vascular cells using isolated specimens and cells grown in tissue culture. (D3)	SAME (WAS D1)	11 [1]	13	0	9	13
4. Develop new animal models of vasoproliferative retinopathies. (D4)	SAME (WAS D2)	5	8	0	4 [1]	5
5. Investigate approaches that prolong retinal survival time after major vascular occlusion and permit restoration of retinal function. Investigate methods for revascularizing areas of ischemic retina. (D5)	SAME (WAS D3)	1	3	0	0	0 [1]
6. Improve noninvasive methods for determining oxygen saturation in retinal blood vessels. (D6)	SAME (WAS D4)	0	4	0	0	0

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF RETINA/CHOROID: DIABETIC/SICKLE CELL RETINOPATHY & OTHER VASC. ABNORMAL. (1-E2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
7. Encourage basic research which will lead to the pharmacological management of retinal vascular disorders. (D7)	SAME (WAS D5)	0	3	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		28 [1]	36	45	55 [1]	53 [1]
TOTAL FOR SUBPROGRAM		48 [2]	61	45	74 [1]	73 [2]
(% OF PROGRAM)		(12.5)	(11.5)	(43.7)	(16.9)	(15.6)

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Inflammatory Disorders

2

Perspective on Recent Research

Investigation of the mechanisms underlying ocular inflammatory disease has great significance, not only to the ophthalmic immunologic community, but to immunologists in general, since it is possible to dissect immune responses in the eye which are sometimes impossible to evalute in other organ systems. Tools that permit a more effective evaluation of both clinically obtained specimens and laboratory models have been developed. The use of monoclonal antibody technology to better define immune cell components has been a cornerstone of these advances. This has been coupled with other methodology such as T-cell cloning and molecular biology. Recent observations also make clear that ocular immunology may also have importance for other areas of ophthalmic research.

Progress in Areas Discussed in the 1983-1987 Plan

In the period since publication of the Plan, several noteworthy accomplishments have been made in research on ocular inflammatory disorders.

There has been improved definition of uveitogenic antigens in the eye. Several researchers have begun to split the retinal S-Ag molecule in order to identify the uveitogenic moiety[1,2] as well as a potential "protector" or "suppressor" moiety, which has been reported in other autoimmune diseases. Additionally, the S-antigen has been cloned. The full potential of this accomplishment has yet to be exploited.[3] A second retinal antigen, intraretinal binding protein, has been isolated and cloned as well. This antigen will induce a different intraocular inflammatory event than that produced with S-Ag immunization.[4]

HLA and other genetically determined markers in uveitis have been implicated in several disorders. A role for endotoxin or other bacterial cell wall antigens has been implicated in B27-associated anterior uveitis[5], as have Gm allotype markers.[6]

The utilization of monoclonal antisera directed against ocular tissue and immune system components has added greatly to our knowledge of the intraocular inflammatory response. This has been a particularly useful tool in the evaluation of frozen ocular tissue, permitting for the first time a delineation of lymphocyte subsets in the human eye. This has been applied particularly to the cellular infiltrate seen in sympathetic ophthalmia, and also in retinal biopsy specimens of cases of undefined uveitis that pose a therapeutic dilemma.[7-9]

New therapeutic modalities in the treatment of ocular inflammation have burgeoned. Studies of the use of cyclosporine in the treatment of human uveitis have passed from the case history phase to that of a randomized masked trial, the first of its kind in this field.[10] Laser therapy has been shown effective for subretinal neovascular nets in the presumed ocular histoplasmosis syndrome.[11]

Immune studies have been extended to other diseases of the posterior segment.[12] In retinitis pigmentosa (RP) various cellular immune reactions have been noted, including S-antigen responses, an altered ability to produce normal amounts of gamma-interferon, and diminished Class II antigens on the macrophages of RP patients.

Most of the accomplishments in this subprogram since publication of the Plan were due in large part to active collaboration between the ophthalmic community and the immunologic, molecular biologic, and other scientific communities. This underscores the need for further integration of eye research with that of the larger immunological research community but also points up the necessity of more rigorous immunologic training for the ophthalmic researcher. Unfortunately, ocular immunology is largely unknown to the greater immunological research community. This is significant for eye research because greater contact between ophthalmic and other immunologic investigators could stimulate ocular immune research and put in on a par with that of immunologic research in other fields of medicine. Such interaction would be enhanced if more ophthalmic researchers were better trained in immunology.

New and Developing Areas of Research

The rapid growth of molecular biology in the past decade has resulted in a whole range of approaches that can be integrated with ocular immunology. An example is the cloning of the S-antigen mentioned above. Advancing monoclonal antibody technology will continue to be used to explore the immune response in the eye. It can also be applied to studies of the role of ocular tissue in the mediation of the immune response. It should be possible to establish new therapeutic modalities by looking, for example, for natural specific mediators. It may be possible, if necessary, to apply T-cell hybridoma technology to this type of problem.

Balance of Effort Within Subprogram

In FY 1981, 14 grants were funded in this subprogram. The Plan recommends nearly a doubling of the grants awarded in this field by FY 1983, reflecting the importance of and recognized potential for expanded investigation in this field. However, in FY 1984, only 13 projects actually were funded. Five of the nine projects falling into the Program Base were in one category: utilization of inbred strains of animals to produce models of chronic or recurring inflammatory diseases (B2), whereas all four of the projects listed under Program Development Priorities were in just one of the five priorities listed: Determine the role of autoantigens in the induction of chronic inflammatory disease (D4).

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Program Base and Program Development Priorities should be revised to eliminate redundancies and to consolidate related recommendations. The Priorities also need to be revised to reflect new opportunities to apply the newer approaches of molecular biology and genetics. Recombinant DNA technology can now be used to explore gene expression and to uncover basic mechanisms in ocular inflammatory disorders. There should be a greater emphasis on controlled clinical trials for therapy of both endogenous and infectious uveitis. These can be used to develop more specific medications and to refine drug delivery systems. Finally, a greater emphasis is required in the exploration of the immune response in the eye. New methods are needed to diagnose ocular inflammatory disorders and to determine the role of the immune system in other ocular disorders.

Recommended Changes in Program Base and/or Program Development Priorities

Some overlap exists in several of the Plan's recommendations in this subprogram. An amalgamation of these recommendations is indicated, as shown in the revised Resource Table.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF THE RETINA AND CHOROID: INFLAMMATORY DISORDERS (1-E3)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Applications FY 1983-84 Funded	Applications FY 1983-84 Percent
PROGRAM BASE								
1. Develop and improve methods for the diagnosis of specific inflammatory diseases. (B1)	1	2	0	0	1	0	0	
2. Utilize inbred strains of animals to produce models of chronic or recurring inflammatory diseases. (B2)	3	3	2 [1]	3	5	3	2	66.7
3. Determine the epidemiology, pathogenesis, and nature of the uveal response to infectious agents. (B3)	4	4	3	3	1	2	2	100.0
4. Analyze the immunopathogenic responses in uveitis. (B4)	5	5	6	5	2	3	0	
5. Develop drug delivery systems that optimize the delivery of pharmacological agents to target sites in the retina or uvea. (B5)	0	1	0	0	0	1	0	
TOTAL FOR PROGRAM BASE	13	15	11 [1]	11 [0]	9 [0]	9	4	44.4
PROGRAM DEVELOPMENT PRIORITIES								
1. Search for the etiology of various inflammatory diseases caused by infectious agents. (D1)	0	1	0	0	0	0	0	
2. Establish the usefulness and safety of vitreous and chorioretinal biopsies. (D2)	0	1	0	0	0	0	0	
3. Make maximum use of surgical specimens and autopsy eyes to obtain information on pathogenetic mechanisms. (D3)	0	2	0	0	0	0	0	
4. Determine the role of autoantigens in the induction of chronic inflammatory disease. (D4)	1	4	3	3	4	12	3	25.0
5. Conduct randomized controlled clinical trials of antimicrobial and anti-inflammatory agents. (D5)	0	2	1	1	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	10	4 [0]	4 [0]	4 [0]	12	3	25.0
TOTAL FOR SUBPROGRAM	14	25	15 [1]	15 [0]	13 [0]	21	7	33.3
(% [illegible] PROGRAM)	(3.7)	(5.0)	(3.9)	(3.8)	(3.4)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF THE RETINA AND CHOROID: INFLAMMATORY DISORDERS (1-E3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Analyze the mechanisms leading to intraocular inflammatory disease and its sequelae such as glaucoma, using autoantigens as well as inbred laboratory models, naturally occurring animal models, and infectious agents. (B1)	COMBINES OLD B1, B2, D1, D4 [DELETED OLD B3, B4, B5]	12	9	0	12 [1]	12
TOTAL FOR PROGRAM BASE		12 [0]	9	0	12 [1]	12 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop and improve methods to define and diagnose ocular inflammatory disease and to determine the role of the immune system in other ocular disorders. This would involve techniques such as retinal biopsy, new methods for detecting an infectious etiology, and immunohistopathology. (D1)	NEW (COMBINES D1, D2)	2	10	0	1	2 [1]
2. Conduct controlled clinical trials for therapy of both endogenous and infectious uveitis in order to develop more specific medications and precise drug delivery systems. (D2)	MORE SPECIFIC (WAS D5)	0	0	8	0	1
3. Utilize recombinant DNA technology to explore gene expression and basic mechanisms in ocular inflammatory disorders. (D3)	NEW	0	5	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	15	8	1 [0]	3 [1]
TOTAL FOR SUBPROGRAM		14 [0]	24	8	13 [1]	15 [1]
(% OF PROGRAM)		(3.7)	(4.5)	(7.0)	(3.0)	(3.2)

Tumors

3

Perspective on Recent Research

Investigations of intraocular tumors have concentrated on the two most common intraocular malignancies—uveal melanoma and retinoblastoma. Both tumors have features that make them unique and appropriately under the purview of the National Eye Institute. Uveal melanoma carries a prognosis strikingly different from skin melanoma, and unlike skin melanoma, it has a prognosis dependent upon the cytologic features of the tumor cells. Retinoblastoma is the prototype of hereditary human neoplasms: 90 percent of those who inherit the mutant retinoblastoma allele develop the tumor. Explaining these idiosyncrasies, and others characteristic of these tumors, requires studies employing a spectrum of technologies. With regard to uveal melanoma, there is controversy over the optimal mode of therapy. Current laboratory research in melanoma focuses on the relationship between tumors and immunological and biochemical processes. With regard to retinoblastoma, evidence is accumulating that tumor-predisposing mutations at the retinoblastoma locus are important in this tumor and its associated neoplasms, such as osteosarcoma. Recent retinoblastoma studies are highlighted by the demonstration that mutant tumor-predisposing alleles at the retinoblastoma locus are recessive at the cellular level and by in vitro and in vivo data that retinoblastoma cells are able to express phenotypic characteristics of a variety of retinal cell types.[4,5]

Progress in Areas Discussed in the 1983-1987 Plan

The National Eye Institute has played an important role in supporting a number of projects in this subprogram that have shed light on issues raised by the Plan. This is especially true in the case of retinoblastoma. Recombinant DNA studies and esterase D linkage studies currently funded appear to be within a few years of the development of a reliable test to detect carriers of the retinoblastoma gene in families with hereditary retinoblastoma.[1-3] Similar technologies have provided an understanding of the role of chromosome 13 deletion in retinoblastoma, and the current thinking is that the tumor-predisposing mutations at the retinoblastoma locus are recessive at the cellular level.[4,5] Evidence supporting an embryonic retinoblast as the cell of origin of retinoblastoma has also been published. Several groups are actively involved in efforts to isolate and characterize the retinoblastoma gene.[7,8] Lee and his colleagues were the first to report the nucleotide and predicted amino acid sequences of the gene.[8]

With regard to melanoma, the culturing of human uveal melanoma cells has been demonstrated.[9] If confirmed, this should open the door to a multitude of productive studies of new diagnostic and treatment modalities for this tumor, including those using monoclonal antibodies.

Until recently the almost universal treatment of primary choroidal melanoma has been enucleation. Concerns regarding tumor cell dissemination and metastasis have resulted in a search for alternative treatments. At present, the most widely used non-enucleation therapy is radiation. Although preliminary data concerning radiation are promising, assessment of treatment efficacy is confounded by referral bias, incomplete patient followup, and followup for relatively short periods of time. To assess the potential role of radiation as a life-preserving as well as sight-preserving treatment, clinicians and scientists from major North American medical centers are cooperating in the NEI-supported Collaborative Ocular Melanoma Study.

New and Developing Areas of Research

Recombinant DNA and monoclonal antibody technology are advancing at an explosive pace. Through molecular genetics research, various human and viral genes important in malignant tumors have been isolated, and the cellular roles played by these genes and their products are under intensive study. Studies of retinoblastoma have uncovered a new class of oncogene, i.e., one where recessive mutations predispose to malignancy.[4,5] Monoclonal antibodies have played a key role in demonstrating the various ways a retinoblastoma cell can differentiate in tissue culture, thereby elucidating the cell of origin of the tumor.[6] The NEI should strongly encourage the further use of these new scientific techniques for the investigation of both retinoblastoma and uveal melanoma.

Epidemiologic and genetic studies of retinoblastoma and melanoma must be re-emphasized, especially in light of the recent dramatic increase in the incidence of cutaneous melanoma.[9] Mortality from melanoma of the skin has increased faster in the United States than any other malignancy save lung cancer in women.[10] Although such a corresponding increase in uveal melanoma is not thought to have occurred,[12] the risk factors predisposing an individual to uveal melanoma or retinoblastoma are little known and little studied. Such studies must receive support.

Advances in biophysics, especially in nuclear magnetic resonance imaging technology, now hold the prospect for the noninvasive diagnosis of intraocular malignancies. Studies of the cellular metabolism of tumors in vivo are also now possible, both before and after various types of therapy.

Balance of Effort Within Subprogram

In FY 1984 The National Eye Institute funded 17 research project grants for studying ocular tumors and one additional small grant. The discrepancies between the Plan's recommended number for FY 1983 (29) and the actual number awarded in FY 1984 primarily involve four categories discussed below. In two out of the four cases, the discrepancies can be considered partly due to poorly defined categories.

In the first category of the Program Base, (Bl): "Continue basic and clinical research on the pathogenesis, diagnosis, and treatment of ocular tumors", the Plan recommends 5 grants for FY 1983, a decrease of 6 from the FY 1981 level of 11. Yet there were 9 grants (including the small grant) funded in FY 1984 in this category. Of the 9, 3 were devoted to the morphologic study of tumor cell lines. These grants could equally well be listed under category B2, making the difference between recommended and funded grants less striking. The National Eye Institute should continue to deemphasize but not entirely eliminate projects solely devoted toward the study of the histopathology of eye tumors.

In category B4: "Establish cell lines for basic studies on the pathogenesis and treatment of retinoblastoma," two grants were recommended for FY 1983, but none was funded in FY 1984. However, one grant listed in category B3 and one listed in category D2 deal with the development of retinoblastoma cell lines. These grants could equally well be listed in this category, bringing the number of funded grants to equal the number recommended by the Plan. Hence, the discrepancy here is mainly due to unavoidable problems in categorizing grants that may relate to two or more categories but must be placed in only one of them.

The first Program Development Priority, Dl: "Establish prospective, randomized, controlled clinical trials of new treatments for patients with ocular melanomas", was stressed in the Plan as needing considerable emphasis with a recommendation that 10 grants of this nature be funded. Only one such project was funded in FY 1984, although this one appears to be of exceptional quality. This avenue of research remains as important as when the Plan was written. The National Eye Institute should also encourage projects designed to discover any potentially avoidable environmental agents or practices which predispose to retinoblastoma or melanoma.

In the third Program Development Priority, D3: "Develop animal models of ocular melanoma for use in immunologic, biochemical, and therapeutic studies," no grants were funded in FY 1984, although the Plan recommends three. In view of the success of tumor cell culture, recombinant DNA technology, and immunological studies in elucidating cellular processes taking place in human tumors, it is advisable to continue to limit the number of projects designed to develop animal models for human eye tumors to three or less.

The above four categories were the only ones with major discrepancies between the number of recommended and funded grants. All other categories are in approximate agreement with the recommendations listed in the Plan.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

A number of potential areas for research are described in the text of Chapter 3 of the *Report of the Retinal and Choroidal Diseases Panel*, but are not listed in the Program Base or Program Development Priorities. For example, the Resource Table for this subprogram has no category specifically defining the need for epidemiologic studies of retinoblastoma and melanoma, yet the importance of and need for such studies is repeatedly stressed in the text. Additional areas not listed in the Resource Table are studies of the natural history of melanomas, better methods of treating retinoblastoma, the role of chromosome 13 deletions in the formation of retinoblastoma, and the role of viruses in retinoblastoma. Many types of research are recommended for both melanoma and retinoblastoma, such as establishment of tumor cell lines, immunologic studies, and epidemiologic studies.

Recommended Changes in Program Base and/or Program Development Priorities

Changing the organization of the Resource Table so that there is no longer a major division between melanoma and retinoblastoma is appropriate. In addition, studies of other rarer intraocular tumors, such as adenocarcinoma of the pigment epithelium, hemangioblastoma of the retina, and medulloepithelioma would be included in categories not specifically and exclusively directed toward one tumor. Certain categories could be broadened to include metastases to the eye (the most common tumor involving the eye). The new Program Base and Program Development Priorities have been rewritten to reflect these recommendations.

Changes have also been made in the Program Base and Program Development Priorities in response to the new developing areas of research discussed above. There is additional emphasis on recombinant DNA research and molecular genetic studies on all intraocular tumors. Such studies had been listed previously as a Program Development Priority only for retinoblastoma. The new advances in nuclear magnetic resonance technology should be applied to studies of intraocular tumors. Immunologic studies of tumor related antigens continue to be recommended. These areas are now listed as specific Program Development Priorities in this subprogram.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF THE RETINA AND CHOROID: TUMORS (1-E4)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Continue basic and clinical research on the pathogenesis, diagnosis, and treatment of ocular tumors. (B1)	11	5	12	12	8 [1]	14	4	28.6
2. Establish continuous cell lines of human choroidal melanoma cells in tissue culture and study human ocular tumors for causative factors and treatment modalities. (B2)	0	1	0	0	1	3	1	33.3
3. Conduct morphologic and biochemical studies of retinoblastoma to determine its cellular origin. (B3)	0	1	1	2	1	3	1	33.3
4. Establish cell lines for basic studies on the pathogenesis and treatment of retinoblastoma. (B4)	1	2	0	0	0	2	0	
TOTAL FOR PROGRAM BASE	12	9	13 [0]	14 [0]	10 [1]	22	6	27.3
PROGRAM DEVELOPMENT PRIORITIES								
1. Establish prospective, randomized controlled clinical trials of new treatments for patients with ocular melanomas. (D1)	0	10	1	0	1	4	1	25.0
2. Characterize the nature of tumor-specific immune competence in treated and untreated patients. (D2)	2	3	3	2	2	2	0	
3. Develop animal models of ocular melanoma for use in immunologic, biochemical, and therapeutic studies. (D3)	2	3	1	1	0	0	0	
4. Study genetic factors involved in the development of retinoblastoma. (D4)	2	4	2 [1]	3 [1]	4	5	4	80.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	6	20	7 [1]	6 [1]	7 [0]	11	5	45.5
TOTAL FOR SUBPROGRAM	18	29	20 [1]	20 [1]	17 [1]	33	11	33.3
(% OF PROGRAM)	(4.7)	(5.9)	(5.1)	(5.1)	(4.4)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

VASCULAR, INFLAMMATORY, NEOPLASTIC DISORDERS OF THE RETINA AND CHOROID: TUMORS (1-E4)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Conduct morphologic studies of ocular tumors, giving special attention to light- and electron- microscopic features which predict prognosis. (B1)	MORE SPECIFIC (INCLUDES OLD B3)	4	5	0	3 [1]	3
2. Establish cell lines and animal models of uveal melanoma and retinoblastoma. (B2)	SIMPLIFIED (INCLUDES OLD B4,D3)	3	3	0	2	2
3. Study the tumor-related antigens important in the immunologic responses to eye tumors. (B3)	NEW [DELETED OLD B1]	3	3	0	3	2
TOTAL FOR PROGRAM BASE		10 [0]	11	0	8 [1]	7 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Conduct molecular genetic studies to determine the nature of inherited predisposition to retinoblastoma and uveal melanoma and the role of oncogenes in ocular tumors. (D1)	NEW (INCLUDES OLD D4)	4	9	0	6	6
2. Conduct biochemical and nuclear magnetic resonance studies to explore the metabolic pathways characteristic of tumor cells. (D2)	NEW (INCLUDES OLD B3)	0	4	0	0	0
3. Determine through epidemiologic studies the risk factors which predispose to uveal melanoma, retinoblastoma, or other ocular tumors and whether the incidence of these tumors is increasing. (D3)	NEW (INCLUDES OLD D1)	2	4	0	2	2
4. Explore the risks and benefits of various avenues of therapy for the tumors, including hyperthermia, radiation, chemotherapy, and immunotherapy. (D4)	MORE SPECIFIC (WAS D1) [DELETED OLD D2]	1 [1]	0	30	23 [1]	27
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		7 [1]	17	30	31 [1]	35 [0]
TOTAL FOR SUBPROGRAM		17 [1]	28	30	39 [2]	42 [0]
(% OF PROGRAM)		(4.4)	(5.3)	(29.1)	(8.9)	(8.9)

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DEGENERATIVE DISORDERS OF THE RETINA

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Developmental and Hereditary Disorders

4

Perspective on Recent Research

Research on retinitis pigmentosa and other allied retinal disorders has accelerated greatly over the last few years. Cell biologists, biochemists, and neurobiologists have brought their contemporary laboratory expertise to bear on many forms of retinal degeneration in laboratory animals, retinitis pigmentosa in humans, and donor eye tissues. Many laboratories have collaborated to share patient data, donor eye tissues, and unpublished findings. Through these collaborative efforts an explosion of new knowledge of possible retinal degenerative mechanisms has occurred in the last few years. The importance of refining epidemiological, analytical, and diagnostic techniques that are available in the clinic have also led to the merging of laboratory and clinical studies in this field. Recently, use of molecular genetic techniques has resulted in the localization on the X-chromosome of the gene that causes one form of retinitis pigmentosa. Thus, research in this area is rapidly progressing in important experimental directions that did not even exist only a few years ago. This is an exciting area of investigation that should produce major advances.

Progress in Areas Discussed in the 1983-1987 Plan

Noninvasive testing using psychophysical and electrophysiologic techniques. Advanced visual testing procedures are essential for the early diagnosis of inherited retinal disorders, as well as for quantitating the progression of the degenerative process. Precise measurements of visual field and sensitivity changes will be essential for evaluating treatment effects in any clinical trials that aim to retard or slow the progression of these disorders. To this end, a variety of studies have been reported since 1981 which have greatly increased the resolution of noninvasive testing procedures.[1-5]

Clinical studies. Clinical studies of the treatment of gyrate atrophy patients using dietary restrictions or vitamin B_6 supplementation as a means of retarding the progression of this disease have continued. In addition, a new clinical trial has been initiated to evaluate the effect of certain metabolites on the progression of retinal degeneration in retinitis pigmentosa patients.

Evaluation of tissues or body fluids for evidence of systemic defects related to inherited retinal degenerations. The specific changes in the retina and choroid accompanying gyrate atrophy are the result of a systemic imbalance in ornithine metabolism. Tissue and blood levels of ornithine in gyrate atrophy patients are 10 to 15 times higher than normal due to a defect in ornithine aminotransferase. Although the various forms of retinitis pigmentosa may be the direct result of specific defects in genes that are expressed uniquely in the retina or pigment epithelium, systemic disorders should not be ruled out, and studies of blood, urine, and other samples that look for possible imbalances in metabolites should be encouraged.

An elevation of blood levels of lipid and lipoprotein in RP patients above age 35 has recently been reported.[6] These studies augment the reports on hyperlipidemia in RP patients which appeared during the 1960s. These findings suggest that an imbalance in lipid metabolism may be associated with retinitis pigmentosa. Additional studies in this area are needed to determine if hyperlipidemia is causally related to the disease process in specific forms of retinitis pigmentosa.

Defects in the immune system have also been implicated in certain inherited retinal diseases. In studies of retinitis pigmentosa patients, various cellular immune reactions have been noted, including the presence of circulating retinal antigens, an altered ability to produce normal amounts of gamma-interferon, diminished Class II antigens on macrophages, and low levels of T-lymphocytes.[7-9]

Studies of human donor eyes with inherited retinal degeneration. Several studies utilizing eye tissues from donors with inherited retinal diseases have been reported since 1981. Ultrastructural studies of tissues from an eye with autosomal dominant form of RP revealed near normal central retina and degenerate peripheral retina coincident with prominent bone spicule pigmentation. Choroidal vasculature was abnormal throughout the eye and virtually absent in the periphery where retinal degeneration was most pronounced. This suggests that the degenerative changes present in the retina were secondary to alterations in the choroid.[10] Additional metabolic studies with tissues from this same eye revealed reduced protein synthesis in the photoreceptors from the nondegenerate region of the central retina,[11] and the vitamin A content of the retina and pigment epithelium were below normal levels.[12] Because the demonstration of these abnormalities in a single eye are unique findings, additional studies with more RP donor tissues will be required before a causal relationship can be established.

Studies of inherited retinal degenerations in animal models. Although human donor tissues have become available for laboratory study on a limited basis during the last few years, animal models with retinal degeneration continue to be the most reliable source of tissues for studies of inherited retinal disease. Studies are underway on a variety of species with inherited retinal disorders, including rodents, chickens, dogs, and cats.[13-19]

Detection of carriers of inherited chorioretinal diseases and prenatal diagnosis. Conventional linkage studies—that is, studies that test genetic markers such as APO and Rh for cosegregation with disease genes in large families—have met with limited success in characterizing retinal and choroidal diseases. One form of autosomal dominant retinitis pigmentosa has been linked tentatively to Rh on human chromosome l, and atypical vitelliform macular dystrophy has been linked to GPTI on chromosome 16. These linked markers are potentially useful in localizing the disease to specific chromosome regions but conventional genetic markers have two major limitations: there are very few of them, and once a linkage is demonstrated there is no obvious method for further investigation of the disease locus.

By contrast, there are now several hundred polymorphic genetic markers, known as restriction fragment length polymorphisms or RFLPs, which are detected using DNA probes.[20] There are several RFLPs mapped to each human chromosome, and many chromosomes, such as the X, are "saturated". That is, given suitable families for study, *any* X-linked disease can be linked to one or more DNA probes. Most importantly, once a DNA linkage has been established, there are direct (though technically difficult) methods to move from the DNA marker to the disease locus itself. Thus, DNA RFLPs not only provide highly informative markers for genetic counseling, but also give access to the specific genetic and biochemical lesions involved.

RFLPs have been linked to several X-linked diseases, such as Duchenne's muscular dystrophy[21] and to the autosomal disease Huntington's chorea.[22] Linked RFLPs have also been recently established for one form of X-linked retinitis pigmentosa,[23] and for X-linked choroideremia.[24]

New and Developing Areas of Research

Linkage analysis using DNA probes. The area of study described above is one that has tremendous potential for facilitating advances in understanding inherited retinal diseases. The application of DNA probes to linkage studies of inherited retinal and choroidal diseases should provide important new insights into the genetics of these diseases. These and related studies are needed to localize the genetic defects on specific chromosomal sites and could lead to further definition of the biochemical defects, detection of carriers, and development of prenatal tests to identify affected individuals. These techniques can be applied in the absence of any knowledge of the biochemical basis of the disease under study, yet offer the potential for isolating the genes themselves. This technology is especially useful for hereditary diseases which are not rare and for which large pedigrees including many affected individuals are available. This is the case for many of the types of retinitis pigmentosa. Studies directed toward the ultimate isolation of a given disease locus typically yield advances in early diagnosis within a few years, and in the long run have the potential to yield sufficient understanding of the disease to allow rational therapy.

Cloning studies. The powerful techniques of molecular genetics offer additional possibilities for studying hereditary retinal and choroidal degenerations as well as learning more about basic retinal functions. Cloning of messenger RNA (mRNA) libraries, isolation and characterization of retinal genes, mapping gene sequences to chromosome regions, and localization of mRNA sequences within tissues using in situ hybridization are among the many new possibilities. Studies are now underway to clone the ornithine-delta-aminotransferase gene from normal subjects and gyrate atrophy patients, which should enable more direct analysis of the processing of these gene products.

With these techniques, several basic questions can be addressed, such as: Are gene sequence deletions or rearrangements involved in the disease? Are there differences in the expression of specific mRNAs in retinitis pigmentosa? Does the cellular compartmentalization of specific mRNAs differ between normal and disease states? Molecular techniques also provide a means for investigation of normal inheritance, development, and regulation of retinal and choroidal genes. This area of study is expanding rapidly and should be well-supported in coming years.

Balance of Effort Within Subprogram

The Evaluation Panel believed that the project levels in this subprogram recommended in the Plan remain adequate except for that involving genetic analysis (D2). Three grants had been previously recommended in this area and three were funded in FY 1984, but the Panel believes that this should be increased to ten.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

No changes are recommended.

Recommended Changes in Program Base and/or Program Development Priorities

No areas require revision at this time; however, the Panel does recommend an increased number of projects over the level recommended in the Plan for this subprogram.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: DEVELOPMENTAL AND HEREDITARY DISORDERS (1-F2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Study animal models of these diseases to define biochemical defects and pathogenetic mechanisms. (B1)	27	29	24 [1]	23 [1]	17	36	11	30.6
2. Define types of retinal malfunction and the short-term natural histories of these diseases using noninvasive techniques. (B2)	8	10	11	10	10	10	4	40.0
TOTAL FOR PROGRAM BASE	35	39	35 [1]	33 [1]	27 [0]	46	15	32.6
PROGRAM DEVELOPMENT PRIORITIES								
1. Search for biochemical defects and pathogenetic mechanisms through studies of patients with degenerative diseases. (D1)	7	10	6	6 [1]	2	10	2	20.0
2. Apply new methods of genetic analysis to studies of patients and animal models of hereditary retinal degenerations. (D2)	0	3	0	0	3	1	1	100.0
3. Develop methods to detect carriers of these diseases and prenatal tests to identify affected individuals. (D3)	0	2	0 [1]	0	0	0	0	
4. Conduct epidemiologic studies on developmental and hereditary diseases of the retina and choroid. (D4)	0	3	0	0	0	0	0	
5. Support therapeutic trials for degenerative diseases of the retina and choroid. (D5)	0	2	0	0	1	1	1	100.0
6. Evaluate the efficacy of new aids for the partially sighted. (D6)	0	0	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	7	20	6 [1]	6 [1]	6 [0]	12	4	33.3
TOTAL FOR SUBPROGRAM	42	59	41 [2]	39 [2]	33 [0]	58	19	32.8
(% OF PROGRAM)	(11.0)	(12.0)	(10.6)	(10.0)	(8.6)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: DEVELOPMENTAL AND HEREDITARY DISORDERS (1-F2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1 Study animal models of these diseases to define biochemical defects and pathogenetic mechanisms. (B1)	SAME	20	30	0	21 [2]	24 [1]
2. Define types of retinal malfunction and the short-term natural histories of these diseases using noninvasive techniques. (B2)	SAME	10	11	0	9	12
TOTAL FOR PROGRAM BASE		30 [0]	41	0	30 [2]	36 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Search for biochemical defects and pathogenetic mechanisms through studies of patients with degenerative diseases. (D1)	SAME	2	12	0	2	3
2. Apply new methods of genetic analysis to studies of patients and animal models of hereditary retinal degenerations. (D2)	SAME	3	10	0	4	7
3. Develop methods to detect carriers of these diseases and prenatal tests to identify affected individuals. (D3)	SAME	0	3	0	0	0
4. Conduct epidemiologic studies on developmental and hereditary diseases of the retina and choroid. (D4)	SAME	0	4	0	0	0
5. Support therapeutic trials for degenerative diseases of the retina and choroid. (D5)	SAME	1	0	3	1	1
6. Evaluate the efficacy of new aids for the partially sighted. (D6)	SAME	0	0	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		6 [0]	29	3	7 [0]	11 [0]
TOTAL FOR SUBPROGRAM		36 [0]	70	3	37 [2]	47 [1]
(% OF PROGRAM)		(9.4)	(13.2)	(2.9)	(8.4)	(10.0)

Macular Degeneration

5

Perspective on Recent Research

The impact of macular disease on affected individuals and on the economy is well recognized in the Plan. Because most cases are associated with aging, it is likely that the impact of macular disease will increase in years to come as the number of aged people in our population increases. Major clinical studies have been and are being conducted to investigate treatments for some types of macular disorders. For most forms, however, fundamental causes are not known, and preventive measures and treatments have not been established. Research in this field should continue to be devoted to understanding basic tissue function in the macular and extramacular retina and to identifying changes in tissue function in pathologic conditions.

Progress in Areas Discussed in the 1983-1987 Plan

Major accomplishments in this subprogram have resulted from the Macular Photocoagulation Study, a multicenter clinical trial of laser therapy for aging-related macular disease and for ocular histoplasmosis. In September 1983, the Macular Photocoagulation Study Group reported the results of the Ocular Histoplasmosis Study (OHS),[1] the purpose of which was to determine whether argon laser photocoagulation is beneficial in preventing loss of visual acuity in eyes with evidence of ocular histoplasmosis and with neovascular membranes 200 to 2500 microns from the center of the foveal avascular zone. Further recruitment for the OHS was terminated because more untreated eyes than treated eyes to date had experienced severe visual acuity loss. At a subsequent follow-up visit (median 18 months), 34.2% of untreated eyes vs 9.4% of treated eyes had lost six or more lines of visual acuity from baseline levels. Follow-up of patients continues in order to assess long-term treatment results.

The Study Group had previously reported that argon laser photocoagulation treatment of neovascular membranes is effective in preventing severe visual loss in patients with aging-related macular degeneration.[2] The NEI has estimated that annual nationwide application of the findings from this study to all eligible patients would save approximately $260 million, 150 times the cost of the study itself.[3] A clinical trial of krypton laser treatment of juxtafoveal neovascular membranes secondary to aging-related macular degeneration, also part of the MPS, is still in progress.

There have been recent efforts to examine cellular changes that might be relevant to macular disease. The continued use of an animal model of subretinal neovascularization[4], studies of barrier and pump functions of the retinal pigment epithelium (RPE)[5-7], and investigations of photic injury to the retina[8-9] all may contribute to our understanding of the mechanisms of macular degeneration. The basic research question in this field, however, remains essentially unstudied: How does the macula differ from non-macular regions of the retina and why is it predisposed to certain pathologies?

New and Developing Areas of Research

With recent improvements in cell culture technology and the development of progressively more "micro" biochemical techniques, questions of retinal regionality are becoming more amenable to study. Cell culture methods, including growth on biological substrates and use of defined media, now permit the maintenance of differentiated functions in vitro. In particular, by applying these and other procedures to the pigment epithelium,[10] it is now possible to examine the differentiated properties of these cells in culture.

Advancements in immunologic localization techniques and in the availability of antibodies (especially antibodies to extracellular matrix macromolecules likely to be found in Bruch's membrane) could be used to detect compositional differences between the macular and extramacular regions and changes within the macula with aging. Early postmortem human eyes might be used more extensively to establish cell cultures of RPE from specific retinal regions and to examine changes in tissue function and structure with aging. Eyes from aged primates might also be used for similar studies and for more experimental approaches to investigation of the macular region.

Balance of Effort Within Subprogram

The Plan recommends a substantial increase (from 18 to 34) in the number of projects in this subprogram by FY 1983. In FY 1984, there were 24 funded projects (including 2 Small Grants for Pilot Projects) indicating a modest increase in funding over FY 1981. However, 13 of the supported grants are components of the multicenter Macular Photocoagulation Study. Only 6 of the 24 studies funded in FY 1984 deal with basic mechanisms of macular degeneration or use animal models to ascertain factors contributing to this disorder. Although a need for a fundamental cell biological approach to causes of macular degeneration was stressed in the Plan, this emphasis is not reflected in the FY 1984 funding pattern.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The first Program Development Priority in the Plan is intended to foster studies to examine the normal and pathologic functions of the tissues involved in macular degenerative disorders: the RPE, the choroid, and the intervening Bruch's membrane. The Plan justifiably recommends a significant increase (from 0 to 5) in the number of grants in this area by FY 1983 because little is known about the fundamental defects that lead to macular pathology. In FY 1984, two grants were supported that address this priority, but one is a Small Grant for Pilot Projects that does not deal with basic structure and function. In general, the same situation applies for the other Program Development Priorities: the Plan recommends a substantial increase in funding devoted to basic studies that continue to be important, but there has been little change in support since FY 1981.

Although research support for basic studies in the Macular Degeneration subprogram is limited, projects supported in other Retinal and Choroidal Diseases subprograms address related needs. Many studies supported by the Retinal Pigment Epithelium subprogram investigate basic functions of the RPE—notably RPE lipoperoxide metabolism and RPE interactions with Bruch's membrane—that are also relevant to macular degeneration. Studies of ocular neovascularization, the blood-retinal barrier, and retinal light damage are also supported in other subprograms, and these projects might also contribute information that will add to understanding the pathogenesis of macular disorders.

Nevertheless, despite this overlap with other subprograms, the Evaluation Panel considers the support of basic studies in macular degeneration inadequate. Continued increases in support in this subprogram to meet the Plan's recommendations would be appropriate. A goal should be to sponsor projects that are particularly relevant to macular degenerations. For example, although a number of currently supported studies investigate retinal neovascularization, choroidal neovascularization is also significant in macular disorders, and factors controlling blood vessel growth in these two regions may differ. A special effort should be made to encourage studies that address the regionality of the retina to attempt to determine why the macular zone is at particular risk.

Recommended Changes in Program Base and/or Program Development Priorities

The Evaluation Panel does not recommend any changes in the Program Base categories in this subprogram from what appears in the Plan. The Panel does recommend restating the first Program Development Priority (D1) to stress comparison of tissue function in the macular region to function in other retinal regions and to incorporate D5 which concerns development of experimental animal models of macular disease. Priority D2 and D3 should, in the Panel's opinion, be left unchanged, while D4 should be reworded to be a slightly broader statement of what appears in the Plan. In the Plan, D4 calls for a search for "extracellular factors" affecting neovascularization, but other factors such as cell-cell and cell-matrix interactions are also likely to contribute to new vessel growth.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: MACULAR DEGENERATION (1-F3)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Continue the Macular Photocoagulation Study and conduct other clinical trials to evaluate treatments for macular disease. (B1)	13	13	13	13	13	0	0	
2. Develop noninvasive techniques to improve detection of early defects in macular function, evaluate therapies, document natural history, and assess drug toxicity. (B2)	2	3	1 [1]	1	2	2	1	50.0
TOTAL FOR PROGRAM BASE	15	16	14 [1]	14 [0]	15 [0]	2	1	50.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Expand biochemical and anatomic studies of Bruch's membrane, the pigment epithelium, and choroid to identify changes in macular diseases. (D1)	0	5	0	1	1 [1]	5	2	40.0
2. Expand studies on the barrier and transport properties of the RPE and capillary endothelium in macular diseases. (D2)	2	4	2	2	2	3	1	33.3
3. Initiate epidemiologic studies of macular diseases to identify possible causative, protective, and aggravating factors. (D3)	0	4	0	1	1 [1]	3	2	66.7
4. Search for and characterize extracellular factors that may initiate or modulate subretinal neovascularization. (D4)	0	2	0	0	0	1	0	
5. Develop experimental animal models of macular disease. (D5)	1	3	3	4	3	4	2	50.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	3	18	5 [0]	8 [0]	7 [2]	16	7	43.7
TOTAL FOR SUBPROGRAM	18	34	19 [1]	22 [0]	22 [2]	18	8	44.4
(% OF PROGRAM)	(4.7)	(6.9)	(4.9)	(5.6)	(5.7)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: MACULAR DEGENERATION (1-F3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Continue the Macular Photocoagulation Study and conduct other clinical trials to evaluate treatments for macular disease. (B1)	SAME	14	0	15	20	18
2. Develop noninvasive techniques to improve detection of early defects in macular function, evaluate therapies, document natural history, and assess drug toxicity. (B2)	SAME	3	4	0	4	3
TOTAL FOR PROGRAM BASE		17 [0]	4	15	24 [0]	21 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Expand studies of Bruch's membrane, pigment epithelium, and choroid. Compare metabolism of the macular region to other retinal regions to determine changes with aging and to identify factors that predispose the macula to disease. Develop animal models, including use of aged primates. (D1)	NEW (COMBINES OLD D1, D5)	2 [1]	10	0	2	2
2. Expand studies on the barrier and transport properties of the RPE and capillary endothelium in macular diseases. (D2)	SAME	1	4	0	2	2
3. Initiate epidemiologic studies of macular diseases to identify possible causative, protective, and aggravating factors. (D3)	SAME	1 [1]	4	0	1	1
4. Investigate the cell biology of subretinal neovascularization. (D4)	LESS SPECIFIC	2	3	0	2	2
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		6 [2]	21	0	7 [0]	7 [0]
TOTAL FOR SUBPROGRAM		23 [2]	25	15	31 [0]	28 [0]
(% OF PROGRAM)		(6.0)	(4.7)	(14.6)	(7.0)	(6.0)

Retinal Detachment and Vitreous Disorders

6

Perspective on Recent Research

The Plan cites improvements in the surgical management of retinal detachment and vitreous hemorrhage as the major recent accomplishment in this field. Since the Plan was published, continued refinements in surgical techniques and instrumentation have led to further advances in the management of these conditions. Nonetheless, information concerning the fundamental vitreoretinal changes that occur prior to and after retinal detachment is lacking, and it will not be possible to develop treatments that interfere with these pathologic changes until the factors that contribute to detachment are elucidated.

Progress in Areas Discussed in the 1983-1987 Plan

Proliferative vitreoretinopathy (PVR) remains the most serious clinical complication in this area. In PVR, cells derived predominantly from retinal glia and pigment epithelium invade the vitreous and establish intravitreal tissue membranes that can detach the retina. Recent work indicates that the ability to detach the retina tractionally is a property common to many cell types[1] and that cell proliferation plays a significant role in promoting detachment.[2] The search for growth factors in the vitreous and other eye tissues that stimulate proliferation has become an active new area of research.[3] These studies should be encouraged because cell proliferation is a major contributor to many vascular and nonvascular ocular pathologies.

A multicenter, prospective, randomized clinical trial has been organized to evaluate the relative merits of intravitreal injection of silicone oil or 20% sulfur hexofluoride gas after vitrectomy in the treatment of proliferative vitreoretinopathy. The National Eye Institute has provided funds for the support of the coordinating center for this trial. Eleven participating clinics will be self-supported.

New and Developing Areas of Research

Fundamental findings in other fields of cell biology regarding cell growth control may prove relevant to eye pathology, and studies should be supported that apply new concepts to ocular cellular proliferation. Investigation of chemoattractants for ocular cells is beginning to receive some attention,[4,5] and factors that stimulate cells, such as those of the pigment epithelium, to migrate from their normal position may play a role in retinal detachment.

As the use of intravitreal drugs—for example antiproliferatives[6,7]—increases, it becomes more important to understand the movement of diffusable substances within the vitreous. Other small molecules whose flux within the vitreous is now unknown might include bioactive substances (such as stimulants of proliferation or migration) that may be involved in controlling fundamental events in retinal detachment or in the maintenance of retinal viability after detachment. Similarly, blood vessel growth may be affected by diffusible substances.

Balance of Effort Within Subprogram

The Plan states the need for continued support of basic studies of the vitreous and increased support for fundamental studies of functions of the vitreous and retina that might influence retinal detachment and retinal viability after reattachment. The Plan recommends an increase from 18 to 27 research grants by FY 1983 with most of the recommended increase going to support the Program Development Priorities. There has been little change, however, in the actual funding pattern in this subprogram in which a total of 18 grants were funded in FY 1984.

The first Program Development Priority (Dl) is to expand studies of abnormal cell proliferation, posterior vitreous detachment, and hemorrhage in retinal detachment. Since FY 1981, there has been an increase from 3 to 6 in the number of grants in this Priority (an increase to 9 is recommended in the Plan), but only 2 of the 6 are primarily devoted to ascertaining mechanisms or factors contributing to vitreal cellular changes that lead to retinal detachment. The other projects use animal models to evaluate therapies such as vitrectomy and intravitreal antiproliferatives. Because determination of causes of retinal detachment remains the most pressing problem in this field, support of projects devoted to this topic is inadequate.

Although an increase was recommended in the second Program Development Priority (D2), there was an apparent decrease in FY 1984 in the number of funded projects in this category that encourages research to determine mechanisms for retinal adherence to retinal pigment epithelium and factors to enhance the viability of the detached retina. This is perhaps a misrepresentation of the actual funding picture because projects in other Retinal and Choroidal Diseases subprograms address similar questions. Some projects in the Retinal Pigment Epithelium subprogram, for example, are devoted to

RPE-neural retina interactions that may be relevant to adhesion.

An increase from 3 to 5 grants was recommended for the number of projects aimed at the third Program Development Priority (D3): to improve instrumentation and new methods for diagnosis and treatment of vitreoretinal disorders. In FY 1984, the number of projects did not increase, but the 3 projects that were funded are major studies that may be adequately addressing defined needs in this area.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Plan's recommendations for Program Development Priorities are generally still appropriate, but movement toward the stated goals is not reflected in the projects currently receiving funding. The major weakness is a dearth of studies on basic structural and functional changes in the vitreous and retina preceding and during retinal detachment and following reattachment.

Recommended Changes in Program Base and/or Program Development Priorities

The Evaluation Panel recommends that the first Program Base category remain the same as that stated in the current Plan. Since 1981 several studies of the vitreous, especially the macromolecular constituents, have provided information on basic vitreous structure and changes with disease.[8-10] This fundamental area should continue to receive support.

The first Program Development Priority (Dl) recommended by the Panel is similar to that stated in the current Plan and emphasizes support for studies in cell growth control as well as abnormal cell migration.

The Panel recommends a new second Program Development Priority, which incorporates the original Program Base category B2, to conduct studies on the vitreoretinal interface. This new Priority reflects an increasing need for studies of the movement of diffusible substances within the vitreous. As basic pathologic changes are identified in the vitreous and retina, more drugs will be delivered into the vitreous compartment. As intravitreal drug use is expanded and as bioactive agents in the vitreous are identified and characterized, it will become important to examine small molecule movement within the vitreous, including binding to and interaction with structural components, to determine factors that might affect access to the retina and other tissues.

The Panel's recommended third Program Development Priority is identical to Priority D2 in the Plan. This Priority and a newly added fourth Priority are suggested in response to a need for information on how to maintain or reestablish retinal function after retinal reattachment. Despite improvements in surgical reattachment of the retina, the visual prognosis is often poor. Information is lacking on factors that promote the development of a functional association between a detached sensory retina and the pigment epithelium.

Support for the development of instrumentation and methods for the diagnosis and treatment of vitreoretinal disorders, the Plan's third development priority (D3), should continue. But, to reflect the panel's overall emphasis on basic research, this priority should be moved to the Program Base.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: RETINAL DETACHMENT AND VITREOUS DISORDERS (1-F4)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Conduct research on properties of the vitreous body and changes in aging, trauma, and disease. (B1)	9	7	9	8	6	12	3	25.0
2. Conduct studies on the vitreoretinal interface. (B2)	1	2	1	1	2	1	1	100.0
TOTAL FOR PROGRAM BASE	10	9	10 [0]	9 [0]	8 [0]	13	4	30.8
PROGRAM DEVELOPMENT PRIORITIES								
1. Expand research on abnormal cellular proliferation, posterior vitreous detachment, and hemorrhage in retinal detachment; develop animal models. (D1)	3	9	4 [1]	4	6	7	5	71.4
2. Determine mechanisms for retinal adherence to retinal pigment epithelium and factors to enhance the viability of the detached retina. (D2)	2	4	1 [1]	1	1	1	0	
3. Improve instrumentation and new methods for diagnosis and treatment of vitreoretinal disorders. (D3)	3	5	2 [1]	2	3	3	2	66.7
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	8	18	7 [3]	7 [0]	10 [0]	11	7	63.6
TOTAL FOR SUBPROGRAM	18	27	17 [3]	16 [0]	18 [0]	24	11	45.8
(% OF PROGRAM)	(4.7)	(5.5)	(4.4)	(4.1)	(4.7)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: RETINAL DETACHMENT AND VITREOUS DISORDERS (1-F4)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Conduct research on properties of the vitreous body and changes in aging, trauma, and disease. (B1)	SAME	4	6	0	2	4
2. Continue improvements in instrumentation and development of new methods for diagnosis and treatment of vitreoretinal disorders. (B2)	MOVED (WAS D3)	4	0	2	5 [1]	4 [2]
TOTAL FOR PROGRAM BASE		8 [0]	6	2	7 [1]	8 [2]
PROGRAM DEVELOPMENT PRIORITIES						
1. Expand research on abnormal cellular proliferation and migration; posterior vitreous detachment and hemorrhage in retinal detachment; develop animal models. (D1)	EXPANDED	6	9	0	4	8
2. Expand research on interactions between the vitreous and adjacent tissues including studies of the movement of cells, small molecules, and drugs; study vitreous factors that affect blood vessel growth. (D2)	NEW (INCLUDES OLD B2)	2	7	0	1	1
3. Determine mechanisms for retinal adherence to retinal pigment epithelium and factors to enhance the viability of the detached retina. (D3)	SAME (WAS D2)	1	5	0	1	1
4. Conduct research to determine changes in the retinal pigment epithelium with detachment and reattachment and to identify factors that stimulate photoreceptors regrowth and a return to normal function of the pigment epithelium after reattachment. (D4)	NEW	1	4	0	1	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		10 [0]	25	0	7 [0]	11 [0]
TOTAL FOR SUBPROGRAM		18 [0]	31	2	14 [1]	19 [2]
(% OF PROGRAM)		(4.7)	(5.8)	(1.9)	(3.2)	(4.0)

Toxic and Environmental Disorders

7

The objectives of this subprogram are to improve the scope and quality of clinical and basic research relating to toxic and environmental disorders of the eye, to gather laboratory and clinical information about such hazards in an efficient manner, and finally to disseminate this information. The Panel that prepared the 1983-1987 Plan believed there was a substantial opportunity to apply modern case-control epidemiological techniques to the problem of toxic and environmental materials that damage vision. At the laboratory level they believed it important to localize the cellular sites of drug action and to determine the mechanisms of toxicity. The Plan recommends taking advantage of the organ and tissue culture methods already developed for retina and lens to develop in vitro screening systems.

In FY 1984, the NEI funded two such studies, classified in this subprogram, on the retinal toxicity of antibiotics and toxins and the use of vitreous fluorophotometry in rat chloroquine retinopathy. However, research on toxic ocular effects was also included within a number of projects classified in other NEI subprograms. For example, research was conducted on the retinal toxicity of various intravenously administered flourescent dyes used in angiographic diagnosis, and on the adverse effects of drugs and poisons on the cornea, lens, aqueous outflow channels, and optic nerve. Research was also conducted on the possible ocular complications of anticancer drugs and the nature of drug metabolizing and detoxifying enzymes that determine the fate of drugs in the eye.

The Evaluation Panel believes that although the research objectives of this subprogram are important and worthy of continued emphasis, they are closely related to those of other, more fully developed basic and applied research areas already covered elsewhere in the Report. The Panel therefore suggests that this subprogram be eliminated as a separate division of the Retina and Choroidal Disease Program and that its objectives and recommendations be integrated with other more appropriate subprograms.

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: TOXIC AND ENVIRONMENTAL DISORDERS (1-F5)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Conduct research on toxic and environmental disorders of the eye. (B1)	2	2	2 [1]	2	2 [1]	6	2	33.3
TOTAL FOR PROGRAM BASE	2	2	2 [1]	2 [0]	2 [1]	6	2	33.3
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop screening systems for ophthalmic toxicity. (D1)	0	2	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	0	2	0 [0]	0 [0]	0 [0]	0	0	0.0
TOTAL FOR SUBPROGRAM	2	4	2 [1]	2 [0]	2 [1]	6	2	33.3
(% OF PROGRAM)	(0.5)	(0.8)	(0.5)	(0.5)	(0.5)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RETINAL DEGENERATIVE DISORDERS PROGRAM: TOXIC AND ENVIRONMENTAL DISORDERS (1-F5)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Conduct research on toxic and environmental disorders of the eye. (B1)	SAME	2 [1]	3	0	2	2
TOTAL FOR PROGRAM BASE		2 [1]	3	0	2 [0]	2 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop screening systems for ophthalmic toxicity. (D1)	SAME	0	2	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	2	0	0 [0]	0 [0]
TOTAL FOR SUBPROGRAM		2 [1]	5	0	2 [0]	2 [0]
(% OF PROGRAM)		(0.5)	(0.9)	(0.0)	(0.5)	(0.4)

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FUNDAMENTAL PROCESSES AND RETINAL DISORDERS

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Retinal Pigment Epithelium

8

Perspective on Recent Research

The retinal pigment epithelium (RPE) is a specialized monolayer of cells interposed between the choroidal capillaries and the photoreceptors of the neurosensory retina. Because the RPE controls the exchange of materials between the photoreceptors and their blood supply, it is as vital to the integrity of the visual process as are the photoreceptors themselves. Its key functions are: (1) role in rhodopsin cycle, (2) barrier between the bloodstream and the photoreceptors, (3) secretion of macromolecules into subretinal space, (4) transport of metabolites to and from the subretinal space and blood supply, (5) fluid transport, (6) retinal adhesion, and (7) phagocytosis and digestion of photoreceptor outer segment tips. If any of these functions are disturbed, the photoreceptors and vision are adversely affected.

Research on the RPE has grown at a rapid rate since the inception of the Plan. Tools have been developed to identify separately the two membranes of this epithelium—apical and basal—and to analyze how they differ functionally. Progress has been made in understanding the interrelationships of the RPE and the neural retina, and particularly, the RPE and the photoreceptors, across a variety of key functions, such as vitamin A metabolism, water transport, electrical activity, and response to disease processes. Because of the research community's great interest in such problems, and the application of such techniques as tissue culture, membrane separation, receptor identification, and molecular genetics, a great deal more should be learned about the RPE in coming years.

Progress in Areas Discussed in the 1983-1987 Plan

There has been a continued growth of research on the RPE since 1981. Progress has been made in all of the areas targeted by the Plan's Program Base and Program Development Priorities for this subprogram. Highlights include the discoveries of the vitamin A binding proteins in the RPE cytosol and interphotoreceptor matrix and speculation on their roles in the rhodopsin bleaching and regeneration cycle.[1,3] Of importance for understanding the role of the RPE in retinal adhesion is a recently developed experimental rabbit model.[4,5] These studies have provided experimental support for the idea that the RPE actively transports or absorbs fluid out of the subretinal space. In studies that measured fluid transport across an isolated RPE-choroid preparation[6,7] it was found that the RPE absorbs fluid in the retina-to-choroid direction, and evidence was gained that fluid absorption is driven by absorption of bicarbonate from the subretinal space. Continued and substantial progress also has been made in developing reliable RPE cell cultures, understanding mechanisms of RPE phagocytosis, understanding the RPE response and role in retinal detachment, and in knowledge of how the RPE contributes to the slow potentials of the electroretinogram.

New and Developing Areas of Research

The time may be right to encourage gene cloning studies on the RPE. RPE cells can be obtained in fairly large numbers either directly, by isolating the epithelium in vitro, or in tissue culture. The techniques of recombinant DNA could now be applied to the RPE with the goal of gene and mRNA isolation for key proteins in normal cells; for example, the retinal binding protein of tha basal membrane and the cytosol retinal binding protein.

Balance of Effort Within Subprogram

In FY 1981, 24 grants were funded in this subprogram. The Plan recommends that 37 grants be funded by FY 1983. The actual number of grants funded in FY 1984 was 27 research project grants plus 2 Small Grants for Pilot Projects. Included among the eight Program Development Priorities for this subprogram is emphasis on molecular mechanisms of RPE-photoreceptor interactions and on transport processes between the RPE and retina. Because this transport occurs across the interphotoreceptor matrix, the need for research in this area is also emphasized. Other Priorities concern the biochemical aspects of RPE function in general, development of tissue culture models, noninvasive methods for testing RPE function, study of the RPE as a potential source of antigens for autoimmune diseases of the retina, and, finally, the influence of endogenous and environmental factors on RPE disease and aging.

There was a ⅓ decrease in the Program Base category on RPE phagocytosis (BI) from 9 grants in FY 1981 to 6 grants in FY 1984. The Program Development Priority concerning RPE transport (DI) was actually fulfilled with an increase from 6 to 9 grants as recommended, with one additional Small Grant for Pilot Projects in this category.

No applications were received or funded in the Program Development Priorities concerning the barrier properties of the RPE (D4) or the RPE as a potential source of antigens for autoimmune disease of the retina (D7).

In FY 1984, there was still only one funded grant on noninvasive tests of RPE function, although 4 were recommended for FY 1983.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

Overall, this subprogram is superbly discussed in the Plan, and in general, the recommendations still anticipate and reflect the most important areas for research.

Recommended Changes in Program Base and/or Program Development Priorities

There is a considerable overlap among this and other subprograms but these, for the most part, already have been identified. Three of the Program Development Priorities in which there are no grants and which are now covered in the other subprograms, D3, D7, and D8, should be removed.

A new Program Development Priority should be added to emphasize the need for recombinant DNA techniques to be applied to the RPE.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: RETINAL PIGMENT EPITHELIUM (1-G2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Investigate molecular mechanisms underlying the rhythmicity and control of RPE phagocytosis and metabolism. (B1)	9	9	6	7	6	8	5	62.5
2. Determine the anatomical and functional relationships between photoreceptors and the RPE. (B2)	3	3	4	4	4	2	2	100.0
TOTAL FOR PROGRAM BASE	12	12	10 [0]	11 [0]	10 [0]	10	7	70.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Analyze special aspects of RPE transport. Characterize biochemical and biophysical properties. (D1)	6	9	6	8	9 [1]	9	5	55.6
2. Study the metabolism of the RPE with particular emphasis on cell isolation, culture, and fractionation methods. Explore the factors which control the properties and functions of the RPE. (D2)	2	4	3	4	3 [1]	10	3	30.0
3. Investigate the physiological and biochemical mechanisms of retinal adhesion and subretinal fluid resorption and their relationship to retinal detachment. (D3)	0	0	0	0	0	0	0	
4. Examine the barrier properties of the RPE and determine if these properties are altered in disease. (D4)	0	2	0	0	0	0	0	
5. Examine the effects of light, age, drugs, and antioxidants on lipofuscin in the RPE cell. (D5)	3	5	1	2	4	3	2	66.7
6. Improve noninvasive clinical tests for RPE function. (D6)	1	4	1	1	1	0	0	

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: RETINAL PIGMENT EPITHELIUM (1-G2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
7. Investigate the RPE as a potential source of antigens for autoimmune diseases of the retina. (D7)	0	1	0	0	0	0	0	
8. Identify, develop, and utilize animal models to study the cellular basis of RPE disease. (D8)	0	0	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	12	25	11 [0]	15 [0]	17 [2]	22	10	45.5
TOTAL FOR SUBPROGRAM	24	37	21 [0]	26 [0]	27 [2]	32	17	53.1
(% OF PROGRAM)	(6.3)	(7.5)	(5.4)	(6.6)	(7.0)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: RETINAL PIGMENT EPITHELIUM (1-G2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Investigate molecular mechanisms underlying the rhythmicity and control of RPE phagocytosis and metabolism. (B1)	SAME	7	9	0	8	6
2. Determine the anatomical and functional relationships between photoreceptors and the RPE. (B2)	SAME	3	3	0	2	3
TOTAL FOR PROGRAM BASE		10 [0]	12	0	10 [0]	9 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Analyze special aspects of RPE transport. Characterize biochemical and biophysical properties. (D1)	SAME	10 [1]	11	0	12	12
2. Study the metabolism of the RPE with particular emphasis on cell isolation, culture, and fractionation methods. Explore the factors which control the properties and functions of the RPE. (D2)	SAME	3 [1]	6	0	5	6
3. Examine the barrier properties of the RPE and determine if these properties are altered in disease. (D3)	SAME (WAS D4)	0	2	0	0	0
4. Examine the effects of light, age, drugs, and antioxidants on lipofuscin in the RPE cell. (D4)	SAME (WAS D5)	4	6	0	5	4
5. Investigate the physiological basis for non?invasive clinical tests of RPE function. (D5)	NEW (INCLUDES OLD D6)	0	4	0	1	1
6. Perform recombinant DNA studies of RPE cells with the goal of isolating genes for key proteins such as the retinal binding proteins. (D6)	NEW [DELETED OLD D3, D7, D8]	0	4	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		17 [2]	33	0	23 [0]	23 [0]
TOTAL FOR SUBPROGRAM		27 [2]	45	0	33 [0]	32 [0]
(% OF PROGRAM)		(7.0)	(8.5)	(0.0)	(7.5)	(6.8)

Photoreceptors, Visual Pigments, and Phototransduction

9

Perspective on Recent Research

Visual Excitation and Phototransduction. Although it would be premature to say that visual transduction is a solved problem, the last five years have witnessed solid progress in unraveling the basic machinery. In the vertebrate rod a clear, sequential relationship of activation has been established for light-activated rhodopsin, GTP binding protein (transducin), and phosphodiesterase. Strong evidence supports the notion that cGMP is an internal messenger in vertebrate transduction.[5,12-15] In an invertebrate preparation (*Limulus* ventral photoreceptor) a substantial case has been made for the involvement of inositol triphosphate in phototransduction.[2-4] Cyclic inositol triphosphate may be even more potent than the non-cyclic compound.[17]

Characterization of Photoreceptor Membranes. An important development is the generation of a series of photoreceptor-specific antisera capable of distinguishing different proteins, e.g., opsin. Additionally, the genetic control of opsin production is being elucidated through identification of the mRNA's involved, and the amino acid sequence and 3D stereochemistry of opsin are being resolved. Placing major emphasis on opsin is logical since it accounts for about 85% of photoreceptor outer segment proteins.

Characterization of Adaptation Mechanisms. Advances in the electrophysiology of photoreceptor adaptation have emerged primarily from studies using the so-called rod suction technique in which a single outer segment is drawn into a close fitting pipette.[18] It has been possible to study the spectral sensitivity, the kinetics of desensitization, and the quantal bumps that are seen near dark threshold.[7,19]

Photoreceptor Transmitters. The identity of photoreceptor transmitter(s) is not yet known with certainty, but there is growing evidence that glutamate is the cone transmitter, at least in some species.[9] Work is proceeding on characterizing the uptake and release mechanisms of glutamate. An exciting development in relation to post-synaptic binding of glutamate is the realization that there are several glutamate receptors, distinguished by their stereochemistry. Drugs that are good analogs for these various receptors (kainate, quisqualate, n-methyl D aspartate) can be used to block selectively synaptic input to different second and third order retinal cells.

Progress in Areas Discussed in the 1983-1987 Plan

There has been considerable recent progress in our understanding of the light-gated conductance of the vertebrate photoreceptor outer segment. It is now clear that the channel is permeable to a large number of monovalent and divalent cations, including calcium. Calcium concentrations are thus enrolled in large part by inward flow through the channel and outward extrusion by a Na/Ca exchange.[8] Additionally, there may be active uptake by internal mechanisms such as the disk membrane. In that regard, it will be important to obtain reliable estimates of the intracellular concentration of calcium.

The channel appears to have a very low conductance compared to standard Na channels in nerve tissue based on noise measurements of membrane patches. In fact, it cannot be ruled out that the channel is some sort of carrier, rather than a pore.

These studies bear on the transduction mechanism and tend to argue against a major role for calcium. Thus, the calcium efflux reported to occur during light may reflect a reduced inflow through the channel while the Na/Ca exchange continues unabated rather than, as previously interpreted, as an expression of calcium release from an intradiskal store. Moreover, at the 1984 Dahlem Conference in West Berlin it was reported that patches of photoreceptor membrane respond directly to GMP, identifying it as the internal messenger. Clearly, these two general areas of endeavor—transduction biochemistry and photoreceptor membrane electrobiology—are beginning to merge as the transduction mechanism becomes clarified.

New and Developing Areas of Research

Molecular approaches to photoreceptor function are playing an increasingly important role in guiding research. The bovine and human rhodopsin genes have been isolated and completely sequenced,[23,24] opening up an entirely new area of investigation. It is now possible to create monoclonal or polyclonal antibodies against specific photoreceptor proteins. In this regard, Barnstable has reported on antisera that distinguish photoreceptors from other retinal cells, rods from cones. An antibody that appears to label exclusively photoreceptor synaptic terminals has been described.[20] The Thy-1 antigen is only expressed by ganglion cells.[21] Monoclonal antibodies to specific components of the rod cell have been obtained and will prove useful in evaluation of the cyclic GMP pathway.[22]

Patch clamp and whole cell clamp studies have amplified greatly our ability to analyze the behavior of the protein complexes (channels) that govern the ionic fluxes across the membranes of retinal cells.[1] A number of different time- and voltage-dependent channels have been identified by means of these techniques in photoreceptor, horizontal, and bipolar cell membranes.[10] The same methods make it possible to study the influence on membrane electrophysiology of neurotransmitter candidates, whether internal or external transmitters and, in the case of the whole cell clamp, to modify the internal composition of the cell.[11]

Balance of Effort Within Subprogram

The present funding levels are adequate, in the context of the recommended and actual number of grants in this subprogram. The Plan recommended a total of 112 grants for FY 1983 and, in fact, 112 were funded in FY 1984, plus 2 small grants for Pilot Projects. This outcome is the more significant when one considers that the total number of grants recommended in the Plan in all areas of the Retinal and Choroidal Diseases program was 492, of which 396 or 80% were actually funded.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Evaluation Panel considered the Program Base and Program Development Priority recommendations to be sufficiently broad to cover the scope of investigations currently underway and to anticipate the probable areas of development in the next few years. The Panel believes, however, that a broader view should be taken of the use of animal models in retinal research. Animal models of disease conditions are important and have been studied with success. But, research will also benefit by identifying models with specific functional deficits that provide insight into one or another aspect of normal photoreceptor function. Gene deficits with visual sequelae, for example, are known in Drosophila mutants that involve single ion channels or other crucial components of the membrane. The possibility for doing molecular genetic research on specific proteins exists and is being pursued with opsin. More molecular genetic approaches of this type are needed in retinal research.

One area of photoreceptor biology, which in the Panel's view is not receiving sufficient attention, is metabolism. Although there have been excellent studies of such specific questions as disk synthesis and renewal, there has not been much done recently with energy metabolism. It still is a mystery why the photoreceptor consumes glucose at a faster rate per mg. protein than any other cell. It may be that due to the poorly vascularized or non-vascularized nature of the inner retina, the photoreceptor layer provides energy yielding compounds to the inner retina in the form of amino acid carbon skeletons. The fate of amino acids released by photoreceptors needs to be documented. The well-known active uptake mechanisms for substances such as glutamate by both neural and glial cells play a role here. A related aspect of metabolism is the synthesis and turnover of photoreceptor transmitter. Work in this area is handicapped by not having the transmitter(s) identified positively. More work needs to be done on the photoreceptor cytoskeleton and its transport capabilities.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel does not suggest any changes in the current Plan's recommendations other than deletion of D3 which is covered in The Developmental and Hereditary Diseases subprogram.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: PHOTORECEPTORS, VISUAL PIGMENTS, AND PHOTOTRANSDUCTION (1-G3)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Investigate the photochemical events of visual excitation by means of chemical, biochemical, and biophysical studies. (B1)	23	21	18	19 [1]	16	35	12	34.3
2. Characterize photoreceptor membrane systems. (B2)	21	20	20	18 [1]	13 [1]	12	8	66.7
3. Investigate the phototransduction process. (B3)	31	28	39 [1]	39	42	48	21	43.8
4. Characterize the adaptation mechanisms that regulate the photoreceptor threshold, speed of response, and dynamic range. (B4)	8	8	9 [2]	7	6	7	0	
5. Investigate the role and mechanism of synaptic interactions between photoreceptors and the cells they innervate. (B5)	7	7	10	10	10	11	5	45.5
TOTAL FOR PROGRAM BASE	90	84	96 [3]	93 [2]	87 [1]	113	46	40.7
PROGRAM DEVELOPMENT PRIORITIES								
1. Investigate photoreceptor metabolism, its control, and metabolic interactions with the RPE. (D1)	18	21	18 [2]	17	16 [1]	20	9	45.0
2. Investigate environmental, nutritional, and other factors that may affect the quality of photoreceptor function, degeneration, and aging. (D2)	4	7	8	10 [2]	9	18	7	38.9
3. Use animal models in attempts to prevent or slow down photoreceptor degenerative processes. (D3)	0	0	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	22	28	26 [2]	27 [2]	25 [1]	38	16	42.1
TOTAL FOR SUBPROGRAM	112	112	122 [5]	120 [4]	112 [2]	151	62	41.1
(% OF PROGRAM)	(29.4)	(22.7)	(31.6)	(30.7)	(29.1)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: PHOTORECEPTORS, VISUAL PIGMENTS, AND PHOTOTRANSDUCTION (1-G3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Investigate the photochemical events of visual excitation by means of chemical, biochemical, and biophysical studies. (B1)	SAME	18	21	0	16	14
2. Characterize photoreceptor membrane systems. (B2)	SAME	13 [1]	20	0	12	11
3. Investigate the phototransduction process. (B3)	SAME	38	30	0	44	51
4. Characterize the adaptation mechanisms that regulate the photoreceptor threshold, speed of response, and dynamic range. (B4)	SAME	6	8	0	2	2
5. Investigate the role and mechanism of synaptic interactions between photoreceptors and the cells they innervate. (B5)	SAME	8	7	0	7	9 [1]
TOTAL FOR PROGRAM BASE		83 [1]	86	0	81 [0]	87 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Investigate photoreceptor metabolism, its control, and metabolic interactions with the RPE. (D1)	SAME	16 [1]	25	0	17	16
2. Investigate environmental, nutritional, and other factors that may affect the quality of photoreceptor function, degeneration, and aging. (D2)	SAME [DELETED OLD D3]	8	9	0	7	5 [1]
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		24 [1]	34	0	24 [0]	21 [1]
TOTAL FOR SUBPROGRAM		107 [2]	120	0	105 [0]	108 [2]
(% OF PROGRAM)		(27.9)	(22.7)	(0.0)	(23.9)	(23.0)

Retinal Organization, Neurotransmission, and Adaptation

10

Perspective on Recent Research

Progress in this area continues to advance at a rapid pace, due in large part to the application of newly developed methods of study. The development of antisera with high specificity against neurotransmitters or enzymes involved in their synthetic or catabolic pathways has made possible the cellular localization of transmitter candidates. Electrophysiological studies of the retina have benefited from the ability to isolate and maintain individual cells in a viable state. The membrane properties of such cells are being elucidated by voltage clamp methods. The results to date have uncovered a variety of time- and voltage-dependent channels as well as electrically coupled channels (gap junctions) and transmitter-gated channels. There is growing evidence that there are not always clear distinctions among these three groups of channels; all may be modulated by transmitters and related chemicals. Finally, system analyses, utilizing increasingly sophisticated stimulation and data analysis methods, have led to the perception that inner retinal neurons do contribute to the pattern electroretinogram.

Progress in Areas Discussed in the 1983-1987 Plan

Pathways for Information Flow. This field has burgeoned since 1981, in large part due to the increasing availability of specific antisera directed against neurotransmitter candidates. Some 30-40 neurotransmitter molecules have been identified in vertebrate retinas; these may be divided further into conventional transmitters, e.g., amino acids, catecholamines, indoleamines, acetylcholine, and peptides.[6] Co-localization of a peptide and a conventional transmitter in the same cell has been reported.[16] The functional role or roles of peptides have not yet been elucidated. They may act as do conventional neurotransmitters to open or close ionic channels, to modulate transmitter synthesis or release, or to alter retinal metabolism. These potential roles are by no means mutually exclusive.

The other major development in this area is the many demonstrations of interaction between transmitter systems, i.e., one transmitter modifies the operation (uptake, synthesis, or release) of another.[7,8,10]

Intracellular Studies of Retinal Pharmacology. This area of research has kept pace with the one above and has taken two divergent paths. One path involves important studies of drug actions on cells in the intact retina. For example, it has been shown that glycine controls transient inhibition of ganglion cells, whereas GABA controls sustained inhibition.[9] The other path concerns studies of solitary cells, isolated from the retina by mechanical or chemical means.[11] Such cells offer the considerable advantage of being free of synaptic inputs. Their passive membrane properties, time and voltage-dependent channels, and susceptibility to any number of transmitters then can be characterized.

Retinal Network Contributions to Retinal Field Potentials. Important advances in network studies have been made with the pattern ERG. Its use has shown that inner retinal neurons, formerly thought to contribute little to the ERG, actually make a substantial contribution.[12] And, as in the above intracellular studies, network studies are complemented by others on cells of the isolated superfused retina, like the Müller glial cell.[13] The regional sensitivity of the latter to changes in extracellular potassium and the resultant current flows through the glial cell are being characterized.[14] The actions of many drugs on the ERG may turn out to be via modulations in extracellular potassium.

New and Developing Areas of Research

There are important research opportunities in the identification and characterization of neurotransmitter systems, the interaction between transmitter systems, and the identification of multiple mechanisms for the control of transmitter synthesis and release.

The neurotransmitter receptor sites are turning out to be much more complex than once thought. These may be multimolecular assemblies with binding sites for a variety of molecules, including the transmitter and its competitive agonist/antagonist as well as anesthetics or neuroleptics and circulating hormones. For example, it was shown recently that N-acetyltransferase, an enzyme that acts on the pathway in which serotonin is converted to melatonin, exists in the eye and acts cyclicly. Melatonin can induce photoreceptor disk shedding under certain conditions, but it also inhibits dopamine release in rabbit retina at remarkably low concentrations.[15] Moreover, the melatonin binding site is distinct from those occupied by conventional agonists/antagonists. These kinds of data may help explain the basis of certain slow rhythms in the eye, e.g., disk shedding, ERG amplitude, and tonic release of neurotransmitters, and they constitute a plausible basis for slow changes in excitability with obvious implications for adaptation.

In sum, characterization of membrane channels and receptor sites, as well as the biochemistry and pharmacology of retinal transmitters, is, in the Panel's view, an important area for future research.

Psychophysical studies of photoreceptor interactions present important research opportunities, particularly in relation to the Program Base category B3 that calls for developing non-invasive measures of retinal function. For example, it is possible to show psychophysically that the rod system inhibits cone flicker responses.[17,18] Interestingly, a similar interaction can be observed in intracellular records of amphibian horizontal cells,[19] indicating a distal retinal mechanism. Thus, psychophysical tests might be applied to normal individuals and patients with a variety of visual disorders on the one hand, while the physiological bases of the interaction mechanisms are sought in animal studies, on the other. Additional fruitful areas for these sorts of correlations are in studies of pattern ERG and color vision.

The use of monoclonal antibodies has added a new dimension to the study of adult and developing retinas because they permit the user to identify cell types or sub-cellular structures in intact or reduced tissues (e.g., isolated cells or cell mixtures). Examples of such antisera with relevance to retinal studies are those directed against photoreceptors (RET Pl, P2, and P3) that label different components of the photoreceptor cell,[1] that which labels a protein found in the incisures of frog photoreceptor outer segments,[2] and an outer segment disk glycoprotein.[3]

In addition, there is now a large library of antisera directed against the cytoskeleton. For example, one such antiserum against glial fibrillary acidic protein (GFAP) can be used to distinguish Müller glial cell cytoplasm from that of neurons.[4] Finally, the first appearance and change in amounts of certain enzymes during development can be studied by immunochemistry. In that regard, the studies of the induction of glutamine synthetase in embryonic chick retina are of interest.[5]

Balance of Effort Within Subprogram

The overall funding for projects in this area is appropriate in view of the intense research activity directed toward retinal circuitry. Intracellular studies have received major emphasis, whereas biochemical and developmental aspects are underrepresented.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Evaluation Panel believes that the Program Development Priorities for this subprogram are well stated in that they cover the scope of research in this field and they identify most of the important lines of approach without being excessively specific. The Panel believes, however, that more emphasis should be put on cell separation and cell culture methods. The full characterization of neural membranes can be achieved best in isolated cells or using membrane fragments from identified cells. This is true for both pharmacological and electrophysiological studies. In the Panel's view, we will need more investigators well-trained in tissue culture methods to pursue studies of single, identified retinal cells or homogeneous populations of such cells. The attendant problems of cell viability, growth, and possible dedifferentiation have to be addressed. The potential payoff is large.

It is worth emphasizing also the possible links between energy metabolism and transmitter release. It might well be that some "neurotransmitters" really turn metabolism on or off as, for example, epinephrine and glucagon do with glycogen metabolism. The counterpart, that metabolites such as ATP are bound at membrane sites and alter conductance, also is known. Possible links of this sort between intermediary metabolism and neurotransmitter systems should be targeted as a growth area.

In general, there should be greater future emphasis in this subprogram on molecular techniques drawn from methods being utilized in the fields of genetics, immunology, cell biology and biochemistry. In the short run, it will be important to draw attention to such methods and their applicability to retinal research. We should encourage collaboration between visual scientists and those trained in other disciplines. In the long term, we would do well to expand the training of scientists who contemplate a career in vision research, so that they may learn and exploit at first hand the new concepts and methods which have carried analysis of cell structure and function to the molecular level.

Recommended Changes in Program Base and/or Program Development Priorities

No major changes are recommended in the current Plan at this time. The Panel recommends, however, that in Program Development Priorities Dl and D3 the use of molecular genetic approaches be specifically encouraged and that the number of estimated projects be increased in Program Development Priorities D3 and D4 to keep pace with the rapid advances and opportunities in there areas.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: RETINAL ORGANIZATION, NEUROTRANSMISSION, AND ADAPTATION (1-G4)

[No. R03, R43, R44 in brackets]

	Projects	Panel Rec.	Projects	Projects	Projects	Applications FY 1983-84		
	FY 1981	FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
PROGRAM BASE								
1. Further analyze the pathways for information flow in the retina; identify specific neurotransmitters and enzymes within neurons and specific cell types. (B1)	13	14	13	15	17 [1]	15	11	73.3
2. Characterize the physiological and pharmacological responses of retinal neurons emphasizing intracellular studies. (B2)	18	18	20 [2]	19	22	20	14	70.0
3. Determine the basis of retinal network contributions to retinal field potentials and visual adaptation; develop noninvasive physiological and psychophysical tests of retinal function. (B3)	15	15	14 [3]	12	12	23	6	26.1
TOTAL FOR PROGRAM BASE	46	47	47 [5]	46 [0]	51 [1]	58	31	53.4
PROGRAM DEVELOPMENT PRIORITIES								
1. Characterize retinal neurotransmitters, receptors the associated metabolic pathways, and the physiological and biochemical effects of neurotransmitters on postsynaptic cells. (D1)	9	11	6	10	8	17	5	29.4
2. Elucidate the physiological, biochemical, and pharmacological properties of retinal neurons using isolated single cells and tissue culture technique. (D2)	3	5	2	1	4	10	4	40.0
3. Determine the factors underlying neurogenesis, synaptogenesis, the development of the neurotransmitter systems, and the onset of retinal function. (D3)	4	5	5	11	16	34	13	38.2
4. Investigate retinal metabolism, especially energy metabolism, and other biochemical processes critical for retinal function. (D4)	2	3	2 [1]	1	2	5	1	20.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	18	24	15 [1]	23 [0]	30 [0]	66	23	34.8
TOTAL FOR SUBPROGRAM	64	71	62 [6]	69 [0]	81 [1]	124	54	43.5
(% OF PROGRAM)	(16.8)	(14.4)	(16.0)	(17.7)	(21.1)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: RETINAL ORGANIZATION, NEUROTRANSMISSION, AND ADAPTATION (1-G4)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Further analyze the pathways for information flow in the retina; identify specific neuro?transmitters and enzymes within neurons and specific cell types. (B1)	SAME	17 [1]	14	0	17 [2]	19 [1]
2. Characterize the physiological and pharmacological responses of retinal neurons emphasizing intracellular studies. (B2)	SAME	22	18	0	22	24
3. Determine the basis of retinal network contri?butions to retinal field potentials and visual adaptation; develop noninvasive physiological and psychophysical tests of retinal function. (B3)	SAME	12	15	0	9	13
TOTAL FOR PROGRAM BASE		51 [1]	47	0	48 [2]	56 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Characterize retinal neurotransmitters, receptors, the associated metabolic pathways, and the physiological and biochemical effects of neurotransmitters on postsynaptic cells; molecular genetic approaches should be encouraged. (D1)	EXPANDED	9	12	0	8	8
2. Elucidate the physiological, biochemical, and pharmacological properties of retinal neurons using isolated single cells and tissue culture techniques. (D2)	SAME	4	6	0	6 [1]	6
3. Determine the factors underlying neurogenesis, synaptogenesis, the development of the neuro?transmitter systems, and the onset of retinal function; molecular genetic approaches should be encouraged. (D3)	EXPANDED	15	16	0	16	16 [1]
4. Investigate retinal metabolism, especially energy metabolism, and other biochemical processes critical for retinal function. (D4)	SAME	2	7	0	1	3
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		30 [0]	41	0	31 [1]	33 [1]
TOTAL FOR SUBPROGRAM		81 [1]	88	0	79 [3]	89 [2]
(% OF PROGRAM)		(21.1)	(16.7)	(0.0)	(18.0)	(19.0)

Glial Cells and the Retinal Microenvironment

11

Perspective on Recent Research

Nervous systems are intimately associated with, and depend for their survival on, the surrounding extracellular milieu and glial cell environment. In the retina, the photoreceptor outer segments are immersed in the relatively large subretinal space, whereas their inner segments and the remainder of the neuronal elements of the retina are embedded in the more tortuous and narrow extracellular spaces of the retina. The most prominent glial element is the Müller cell, which traverses the layers of the retina, surrounds the neuronal elements, and protrudes its apical processes into the subretinal space. These retinal glia serve important metabolic, ionic, and nutritive functions with respect to the retinal neurons. These functions occur across the extracellular spaces that themselves contain an extracellular matrix whose molecular structure and properties must be closely involved with these functions.

Since publication of the Plan, research on the Müller cell has moved center stage. This has been made possible by the development of isolated cell preparations and their study by various electrophysiological and biochemical techniques. In addition, the placement of ion-sensitive microelectrodes in the various extracellular spaces of the retina has provided new information about how the microenvironment changes during light and darkness, and how this affects glial and neuronal cell activity. Detailed studies of the biophysical properties of Müller cells and of Müller cell interactions with neurons by biochemical techniques, and the beginning application of recombinant DNA techniques to glia, will provide exciting new information about glial function in the retina.

Progress in Areas Discussed in the 1983-1987 Plan

There have been many recent advances in our understanding of the role of glial cells in the brain and retina that relate to the metabolism and biophysical properties of Müller cells.[1] In particular, progress has been made in understanding the role that glial cells play in protecting neurons from the relatively large changes in extracellular potassium concentration that accompany neuronal activity. There is substantial evidence that glial cells act to buffer these potassium changes by rapidly moving potassium back and forth between regions of different potassium concentration[2,3] and recent evidence that Müller cells also act in this way.[4] The recent experiments of Newman have also shown that the Müller cell has a non-uniform potassium conductance. In isolated cells it was found that 94% of the membrane conductance resides in the endfoot.[5]

New and Developing Areas of Research

Studies are needed on the roles of Müller cells in both intermediary metabolism and in neurotransmitter turnover. Because glial cells in general have active transport systems for some amino acids and are the exclusive sites of glutamine synthetase and carbonic anhydrase, they are presumed to play a crucial role in ammonia detoxification and, possibly, pH control or chloride/bicarbonate exchange. Particularly in mammalian retina they concentrate glycogen, but the pathways for glycogenolysis are still uncertain, since glucose 6-phosphatase has been demonstrated only histochemically. The route taken by glucose released from Müller cells is unknown: does it re-enter the retina and nourish neurons or is it picked up by the circulation?

Several techniques that have become prominent in neurobiology and cell biology since the Plan was written should be applicable to retina glial cells in the next several years. The ability to obtain preparations of isolated Müller cells has led already to biophysical studies of the cell membranes of these cells. In particular, patch clamp techniques now can be used on these cells so that the channels of the Müller cell membrane can be identified and the differences between areas of Müller cell membranes can be characterized.

In the field of cell biology generally there is a growing interest in the study of cell-to-cell interactions. Cell interactions during development of the retina have been examined for years, but it is now becoming apparent that mature cells in many tissues also communicate with one another by means of both secretory products and plasmalemmal contact. Interactions between neurons and glia are receiving particular attention, and induction of tissue-specific protein synthesis and enzyme activities as well as trophic effects have been noted as a result of neuron-glial association. New research concepts and methods that are being used to study interactions between non-retinal neurons and glia could now be used to evaluate similar cells of the retina. A re-emphasis on studies of cellular interactions might be appropriate for this program at this time. Investigations of trophic interactions could, for example, not only provide information about basic retinal function but also generate information relevant to the maintenance of retinal viability after detachment or following vascular occlusion. (See "Rescue and Regeneration of Neurons in the Optic Nerve and Retina.")

We also can expect that recombinant DNA techniques will be used on Müller cells in the near future to clone genes and cDNA, to identify proteins, and to obtain genes for glial specific proteins already identified. For example, in work elsewhere in the nervous sytem the RNA coding for glial fibrillary acidic protein (GFAP), a specific component of astrocytes, was recently cloned.[6] Such studies could go hand-in-hand with those identifying the specific proteins that act as receptors on the Müller cell membrane and studies identifying Müller cell specific cytoplasmic proteins—perhaps by developing monoclonal antibodies specific for the cells.

Balance of Effort Within Subprogram

The Plan's recommendation for FY 1983 was to expand the number of funded projects in this subprogram from 6 to 9. There has been, however, a decrease in the number of applications received so that that number of funded projects was 5 in FY 1983 and 4 in FY 1984. The current distribution among the various categories of this rather small number of grants remains essentially unchanged from FY 1981. These grants, however, do not adequately reflect the growth of research in this area because of extensive overlap with other subprograms. In actuality, there are more projects on glial cells and the microenvironment than these numbers indicate. For example, several investigators who devote all or part of their time to glial cells are classified in other subprograms. There is also research on the ionic properties of the retinal microenvironment, the extracellular matrix, and the effect of neuronal injury on Müller cells by other NEI-supported investigators whose projects are not classified in this subprogram.

In sum, an attempt to cross-reference cell studies in the various Retinal and Choroidal Diseases subprograms would reveal an extensive overall effort and a considerable rapid growth in the area of glial cells and the retinal microenvironment.

Adequacy and Current Relevance of the Program Base and Program Development

Although not encompassing all of the research in the field, the current Program Base and Program Development Priorities succeed in targeting some essential problem areas for research in this field. The Panel suggests a number of revisions as detailed below.

Recommended Changes in Program Base and/or Program Development Priorities

Changes are recommended in the Program Base and Program Development Priorities to reflect more adequately the subprogram objectives, to emphasize areas of research requiring expansion, and to target potential new areas of investigation. Thus, the revised Program Base underscores the need for research on all essential aspects of Müller cell function and emphasizes studies related to the ERG, intermediary metabolism, and neurotransmitter turnover. The revised Program Development Priorities target biophysical properties of glial cell membranes, metabolic and interactive (glial-neuronal) studies in culture, and recombinant DNA techniques as major areas for research emphasis.

The Program Base category, BI, does not adequately reflect the need for studies undertaken on the role of glia in intermediary metabolism as it relates to neuronal function and in neurotransmitter delivery and turnover. On the other hand, studies of changes in glial properties associated with neuronal degeneration appear to be covered in other subprograms. ("See Rescue and Regeneration of Neurons in the Optic Nerve and Retina.")

Concerning the first Program Development Priority, DI, although a significant number of such studies are covered in other subprograms ("Retinal Pigment Epithelium" and "Retinal Organization") ion-specific electrode investigations of the extracellular environment and intracellular studies on glial cells are essential to understand glial function and glial-neuron interactions. In addition, intracellular recording and patch-clamp studies on glial cell membranes to determine the characteristics of glial ion channels will greatly add to our understanding of glial cell membrane function.

With regard to Priority D2, at the time the Plan was drafted retinal glia could generally be maintained in vitro only as non-propagating cells, so the number of cells available for analysis was few. More recently it has become possible to generate, from animals with avascular retinas, cultures of glial cells that have some limited growth potential. As culture methods improve it will become possible to maintain differentiated function among proliferating populations of glia, and studies of retinal glial cell metabolism can be significantly expanded.

The current Program Development Priorities do not reflect the rapid growth and possibilities for research using recombinant DNA techniques. The applications of such techniques to identify the genes for glial cell-specific proteins and to identify the proteins themselves should be encouraged, and therefore the Panel suggests the addition of a third Priority for this specific purpose.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: GLIAL CELLS AND THE RETINAL MICROENVIRONMENT (1-H1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Conduct studies to isolate and identify the contribution of the Muller cells to the various components of the transretinal ERG and assess changes in glial cell properties associated with neuronal degeneration. (B1)	3	4	3	2	2	0	0	
TOTAL FOR PROGRAM BASE	3	4	3 [0]	2 [0]	2 [0]	0	0	0.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop and utilize ion-specific electrodes for quantitative analysis of extracellular and intracellular activities of essential ions throughout the retina and for studies of mechanisms of ionic buffering. (D1)	1	2	1	1	1	1	1	100.0
2. Expand the use of cell-separation and culture techniques to isolate and maintain viable glial cell populations for metabolic and pharmacological studies and for biochemical studies of neurotransmitter uptake. (D2)	2	3	2	2	1	2	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	3	5	3 [0]	3 [0]	2 [0]	3	1	33.3
TOTAL FOR SUBPROGRAM	6	9	6 [0]	5 [0]	4 [0]	3	1	33.3
(% OF PROGRAM)	(1.6)	(1.8)	(1.5)	(1.3)	(1.0)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: GLIAL CELLS AND THE RETINAL MICROENVIRONMENT (1-H1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Conduct studies on the basic properties of Mueller cells and their contributions to the ERG and their role in intermediary metabolism and neurotransmitter turnover. (B1)	NEW (INCLUDES OLD B1)	2	4	0	1	1
TOTAL FOR PROGRAM BASE		2 [0]	4	0	1 [0]	1 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop and utilize ion-specific electrodes for quantitative analysis of essential ions throughout the retina and for studies of mechanisms of ionic buffering. Expand studies of the biophysical properties of Mueller cell membranes to characterize ion channels. (D1)	NEW (INCLUDES EXPANDED OLD D1)	1	2	0	2	2
2. Improve methods to propagate glial cells in culture for metabolic and pharmacologic studies and to investigate metabolic, inductive, and trophic interactions between glia and neuron. (D2)	NEW (INCLUDES OLD D2)	1	3	0	1	1
3. Utilize recombinant DNA techniques to clone mRNAs and genes and to characterize cell-specific proteins of Mueller cells. (D3)	NEW	0	3	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	8	0	3 [0]	3 [0]
TOTAL FOR SUBPROGRAM		4 [0]	12	0	4 [0]	4 [0]
(% OF PROGRAM)		(1.0)	(2.2)	(0.0)	(0.9)	(0.8)

Rescue and Regeneration of Neurons in the Optic Nerve and Retina

12

Perspective on Recent Research

Neuronal regeneration involves the morphological and functional recovery of damaged neurons. The bulk of current regeneration research in the visual system deals with retinal ganglion cells, which will survive initial transection or crush of their axons. In the case of fish and amphibia, the axons regenerate, reconnect with appropriate brain targets, and recover function.[1] In contrast, damaged mammalian cells fail to regrow and eventually die. The relevant clinical problems include the reduction of initial ganglion cell damage, the stimulation of appropriate axonal growth, and the promotion of selective synaptic connections. Currently, many investigators believe that factors extrinsic to the neuron determine the success or failure of neuronal regeneration.[2] These regeneration-promoting regulators are thought to include growth factors, neuron-glia interactions, and target neuron recognition signals.

The study of these complex cellular interactions requires multi-disciplinary approaches and encompasses much of the neurosciences. Current studies that limit themselves to analysis of degenerating tissues or testing of neuron-stimulating drugs do not offer insights or a sufficient data base to develop rational schemes for treating neuronal injury. At the present time, too little is known about normal brain development or the mechanisms of successful regeneration to offer hope of rapid clinical breakthroughs. The emphasis on fundamental research in this subprogram rather than clinical trials seems appropriate.

Progress in Areas Discussed in the 1983-1987 Plan

The more productive research areas have employed either developing mammalian, regenerating fish, or regenerating amphibian visual systems. They include the following:

Study of Factors that Promote Neuronal Survival and Growth. Since the discovery of nerve growth factor, investigators have sought to isolate other growth or survival factors that may regulate a neuron's development or response to injury.[3,4] Problems in this area include the low levels of neuron-stimulating activity and lack of selective assays to monitor such activity.

For the most part, advances in separation technology such as high performance liquid chromatography continue to outdistance the advances in the biology of growth factors. Rapid screening of factors is usually carried out by in vitro assay. In the last 5 years, significant advances in tissue culture methods for motoneurons, chick ciliary ganglia, fish retinal ganglion cells, and cortical neurons of fetal rodent have offered improved bioassays for the study of growth factors.[5,6,7] Unfortunately, these culture systems are only neuron-enriched and contain contaminating glia. Therefore, the direct action of a putative neuron-specific factor is often in question, for enchanced neuronal growth may reflect the action of stimulated glia.

The second problem arises as bioassay conditions are made more stringent. All too frequently, survival factors are artifacts of tissue culture as so-called "specific" factors are found to be vitamins or common protein supplements. Despite these limitations, good fundamental research is underway in a number of laboratories to isolate neuron-specific growth factors.

Study of Glia and Their Interactions with Neurons. Glia of the central nervous system include astrocytes, oligodendrocytes, and microglia; these cells are important in supporting the growth and development of neurons. For example, axonal growth substantially improves when neurons are placed in a suitable glial environment.[8] Many investigators believe that the glial response to neuronal injury determines in part the success or failure of regeneration.

Two lines of research relevant to the problem of optic nerve regeneration include study of glial growth factors and neuron-glia interactions.

Recent advances in the isolation, identification, and culture of glia has led to potentially important discoveries of factors that promote glial growth.[9,10] Following transection of the mammalian optic nerve, microglia enter the wound site and engulf debris. Astrocyte scar formation follows and neuronal regeneration fails. Peptides recovered from injured brain have been reported to stimulate astrocyte proliferation.[11] Some of these peptides are released by microglia. Such growth factors may be responsible for glial scar formation in injured optic nerve and therefore may influence regeneration of retinal ganglion cells. In the case of developing optic nerve, progenitor cells in the presence of soluble "factors" differentiate into either astrocytes or oligodendroglia.[12] Again, such factors may help to modify the glial environment in injured tissue.

With regard to the study of glia-neuron interactions, the developing and regenerating optic nerves contain glial populations that are distinct from those found in injured non-regenerating nerve. Studies of fetal mammalian and regenerating fish visual systems suggest that glia provide an extracellular environment needed to direct axonal growth.[13,14] It is possible that suitable axon-glia contacts or axon-extracellular matrix interactions are necessary for successful regeneration.

A third area in which progress has been made is the immune response to neuronal injury. Recent studies have linked antibody production as well as cell-mediated immunity to neuronal degeneration.[15]

New and Developing Areas of Research

Study of Factors that Promote Neuronal Survival and Growth. To date, no neuronal growth factor from the central nervous system has been purified to homogeneity. Although it is likely that similar factors may be under investigation by several laboratories, such redundancy in effort deserves increased support. Perhaps the best examples come from the last decade of research on growth factors found in the immune system.[16] Eventually, dozens of factors named by competing laboratories were found to represent a single molecule. This competition was healthy and led to rapid purification and clinical trials of interleukins and interferons. Clinical application of growth factors requires "clean" material in large quantity; the techniques for gene cloning are readily available to produce such material once isolation has been achieved.

Study of Glia and Their Interaction with Neurons. Further study of glia in regenerating, developing, and degenerating neural systems deserves close attention. A recent report describes peptides in the regenerating fish visual system that stimulate growth of oligodendroglia.[17] Laboratories are now investigating whether such peptides promote the regeneration process. Purification of glial promoting factors to homogeneity has not been done. Though such studies have been plagued by the same problems noted for neuronal growth factors, further support is justified.

Further study to characterize the surface components of neurons and glia during cell contacts as well as the constituents of the extracellular matrix in the central nervous system seem appropriate.[18,19] The complexity of these cell interactions will hamper the initial investigations.

Finally, further work on the inflammatory response to brain and optic nerve injury may lead to therapies for reducing neuronal damage.

Study of Target Neuron Interactions. It is generally believed that target cells provide recognition signals to direct synapse formation with regenerating neurons.[20] This last step in the regeneration process, the formation of connections with appropriate target neurons, is the most difficult to investigate due to the subtle nature of the cell interactions and lack of good in vitro models. Some success has been achieved by application of monoclonal antibodies to identify altered surface membranes in regenerating ganglion cells.[21] Perhaps these membrane components interact with target neuron receptors. Binding studies that attempt to show affinity between retinal ganglion cells and target neurons have been hampered by lack of homogeneous neuronal populations.[22] Although application of newly described neuron isolation techniques (microdissection, cell sorting, and gradient buoyant density techniques) may prove useful in obtaining cells for these studies,[5,23] the possibility of isolating selective recognition molecules appears unlikely in the near future.

Examination of both developing and regenerating neural systems suggest that target recognition signals are influenced by neighboring tissues[24] and may be in a constant state of flux.[25,26] Further in vitro study of promotors that regulate cell recognition signals may prove helpful in identifying conditions needed to induce such signals in vivo.

Overall, target neuron recognition appears to be a necessary prerequisite for successful regeneration. The composition of such recognition signals as well as the conditions to induce or maintain these signals are unknown. Emphasis on research to develop in vitro models for regenerating neuron target cell interactions seems necessary. (See Report of the Strabismus, Amblyopia, and Visual Processing Evaluation Panel)

Balance of Effort Within Subprogram

The panel noted that although the Plan recommends that 7 grants be funded by FY 1983 for this area of research, only 4 were funded in FY 1984. However, these projects concern the types of research described above and are at the leading edge of investigation in this field.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The consensus of the Panel was that the primary emphasis in this subprogram must be placed on fundamental research and that multidisciplinary approaches will be required. Accordingly, the Panel recommended that significant changes be made in the general orientation and specific priorities of this subprogram. Further, the Panel recommended that this report on this subprogram be substituted for the original text until the next five-year plan is formulated. A clearer definition of subprogram objectives is needed as is better integration with related subprograms in the Strabismus, Amblyopia, and Visual Processing Program.

Recommended Changes in Program Base and/or Program Development Priorities

The Evaluation Panel recommends major changes in the direction of the subprogram and suggests new priorities, as noted in the accompanying table.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: RESCUE AND REGENERATION OF NEURONS IN THE RETINA (1-H2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop new primate and other adult mammalian models of optic nerve and retinal rescue and regeneration. (D1)	1	3	0	0 [1]	1	2	2	100.0
2. Investigate neuronal-glial interactions in the retina and optic nerve and their relationship to the problem of regeneration. (D2)	0	2	0	0	0	0	0	
3. Expand research on biochemical and physiological processes in the retina and optic nerve to elucidate factors which prevent degeneration and enable regeneration. (D3)	1	2	1	3	3	7	3	42.9
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	2	7	1 [0]	3 [1]	4 [0]	9	5	55.6
TOTAL FOR SUBPROGRAM	2	7	1 [0]	3 [1]	4 [0]	9	5	55.6
(% OF PROGRAM)	(0.5)	(1.4)	(0.3)	(0.8)	(1.0)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

FUNDAMENTAL PROCESSES AND RETINAL DISORDERS: RESCUE AND REGENERATION OF NEURONS IN THE RETINA (1-H2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM DEVELOPMENT PRIORITIES						
1. Isolate and characterize factors which promote the survival and growth of retinal neurons. Develop in vitro systems to permit needed cellular and biochemical analyses. (D1)	NEW	1	3	0	1	2 [1]
2. Isolate and characterize factors which direct retinal glial responses to injury. (D2)	NEW	1	2	0	1	1
3. Investigate neuron-glia interactions and the influence of the extracellular matrix in developing and regenerating retina. (D3)	NEW (INCLUDES OLD D2) [DELETED D1, D3]	2	3	0	2	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		4 [0]	8	0	4 [0]	4 [1]
TOTAL FOR SUBPROGRAM		4 [0]	8	0	4 [0]	4 [1]
(% OF PROGRAM)		(1.0)	(1.5)	(0.0)	(0.9)	(0.8)

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RELATED AREA OF RESEARCH OPPORTUNITY AND NEED

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Noninvasive Techniques in the Study of Retinal Disorders

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Perspective on Recent Research

Improved methods for early diagnosis and more precise localization of retinal disorders is considered a major goal of this subprogram. Many retinal disorders remain diagnostic problems, and there is a need for an expanded effort to develop new noninvasive techniques for the analysis of the ocular fundus. Specifically, the subprogram objectives are to develop improved non-invasive tests of retinal function and to apply non-invasive techniques to improve the prevention, diagnosis, and management of retinal disease in human infants and adults. The Plan points out quite correctly that success in this field will depend on multidisciplinary skills.

Biomedical engineering has been employed to develop several non-invasive techniques for the study of retinal disorders. These include laser-Doppler velocimetry, laser scanning ophthalmoscopy and in vivo spectrophotometry. The instrumentation is complicated and requires a basic science and clinical team to solve the complex electro-optical and protocol problems.

Progress in Areas Discussed in the 1983-1987 Plan

This subprogram has supported the development of the laser-Doppler retinal blood flow device, and the instrument is clearly being used for the benefit of patients with diabetic retinopathy.[1] Although this is the principal example, the existence of the subprogram has indirectly encouraged many to reexamine their priorities and consider noninvasive techniques in the study of retinal disorders.

There are other examples of noninvasive techniques for the study of retinal disorders. The blood velocity in retinal capillaries has been estimated by studying the blue field entoptic phenomenon.[2] Oxygen saturation measurements in retinal vessels have been estimated by noninvasive techniques.[3,4] Fluorescein angiography has been used to measure retinal blood transit times in patients with diabetes.[5] The scanning laser ophthalmoscope has been developed to obtain high resolution images of the retina for the study of structural defects as well as to place precise test stimuli on the ocular fundus for psychophysical studies.[6,7] Fundus reflectometry may give valuable information about the visual pigments, and clinical instruments have been developed to make the measurements.[8]

New and Developing Areas of Research

Noninvasive diagnostic technology continues to advance at an exponential growth rate. Nuclear magnetic resonance (NMR) imaging instruments are being installed in many hospitals around the nation and the imaging they produce is currently as good as that of CAT scans. With further development and use of this equipment, we can expect that the imaging will become even better. More exciting is the application of NMR spectroscopy for the analysis of metabolic function. This technique may enable tumor typing and perhaps one day the evaluation of retinal cell metabolism.

The scanning laser ophthalmoscope is, in theory, an exciting and potentially useful device. It has not given us the image quality that we would like thus far, but it uses very low light levels with little scatter and should give superb images as well as make possible the presentation of precise test stimuli on the ocular fundus. New solid state television cameras combined with optical matrixing should make extremely high resolution with great sensitivity possible. Image processing of these signals is now fairly routine, and software is needed for the proper assessment of ocular fundus disease. Holography continues to be another exciting area of development with potential use in the eye, and it is important to remember that a great deal of work is still necessary to perfect computer-assisted visual field examinations.

Balance of Effort Within Subprogram

In 1981 the National Eye Institute supported 10 grants in this subprogram. The Plan recommends that 18 grants be funded by FY 1983, but only 4 plus one Small Grant for Pilot Projects was actually funded in FY 1984. All of these relate to Program Development Priority D2 which concerns the need to develop noninvasive tests to assess retinal function and localize retinal defects in disease. Two of these grants were for research on the laser Doppler velocimeter. One of the remaining two was in psychophysics and the other in computer-assisted retinal pigment analysis. The Small Grant was awarded for the study of laser speckle. It should be pointed out, however, that 24 grants in other subprograms were classified as developing or utilizing noninvasive techniques for assessing retina and choroid.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The current Program Base and Program Development Priorities are in themselves satisfactory. As stated above, however, extensive overlap exists with many subprogram recommendations in both the Retinal and Choroidal Diseases and the Strabismus, Amblyopia, and Visual Processing Programs. Emphasis on the development and, in particular, the application of noninvasive tests of normal and abnormal visual system function is found throughout the various subprogram reports.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel strongly favors the continued existence of a separate subprogram for noninvasive techniques. Primary emphasis should be placed, however, on the *development* of new techniques and instrumentation. Specific needs of investigators and clinicians should guide this development, but latitude must be given for new ideas. Projects that involve primarily the *application* of noninvasive techniques should be assigned to the other relevant subprograms, where specific needs and opportunities are discussed in detail. The Panel suggested that the Program Development Priorities be changed to reflect these recommendations.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RELATED AREAS OF RESEARCH OPPORTUNITY AND NEED: NONINVASIVE TECHNIQUES IN THE STUDY OF RETINAL DISORDERS (1-K1)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM DEVELOPMENT PRIORITIES								
1. Refine and further develop practical instrumentation for measuring local (focal) ERG and VER and for correlating responses from local ERG and cortical VEP measurements. (D1)	2	4	0	0	0	1	0	
2. Develop improved noninvasive tests to assess retinal function and localize retinal defects in disease. (D2)	8	12	7 [1]	3	4 [1]	20	4	20.0
3. Develop reliable noninvasive techniques for assessing retinal function in infants. (D3)	0	0	0	0	0	0	0	
4. Utilize noninvasive techniques in studies of etiology, pathogenesis, diagnosis, prevention, and treatment of retinal disorders. (D4)	0	0	0	0	0	0	0	
5. Improve and better define means of evaluating retinal function in the presence of opaque media. (D5)	0	2	0	0	0	2	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	10	18	7 [1]	3 [0]	4 [1]	23	4	17.4
TOTAL FOR SUBPROGRAM	10	18	7 [1]	3 [0]	4 [1]	23	4	17.4
(% OF PROGRAM)	(2.6)	(3.6)	(1.8)	(0.8)	(1.0)			

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RELATED AREAS OF RESEARCH OPPORTUNITY AND NEED: NONINVASIVE TECHNIQUES IN THE STUDY OF RETINAL DISORDERS (1-K1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop new techniques and instrumentation for the noninvasive assessment of retinal function. (D1)	NEW [DELETED OLD D1-D5]	2 [1]	10	0	3	5
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [1]	10	0	3 [0]	5 [0]
TOTAL FOR SUBPROGRAM		2 [1]	10	0	3 [0]	5 [0]
(% OF PROGRAM)		(0.5)	(1.9)	(0.0)	(0.7)	(1.1)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RELATED AREAS OF RESEARCH OPPORTUNITY AND NEED: TISSUE ACQUISITION AND DISTRIBUTION, HUMAN DONOR EYES AND ANIMAL MODELS (1-L1)*

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1. Procure, prepare, and distribute postmortem human donor eyes affected with retinal and choroidal diseases; conduct ultrastructural, biochemical, and tissue culture studies; obtain correlations with premortem clinical findings. (D1)	0	0	0	0	0	0	0	
2. Identify, develop, and maintain new animal models of retinal and choroidal diseases. (D2)	0	0	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	0	0	0 [0]	0 [0]	0 [0]	0	0	0.0
TOTAL FOR SUBPROGRAM	0	0	0 [0]	0 [0]	0 [0]	0	0	0.0
(% OF PROGRAM)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)			

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*In evaluating the implementation of the 1983-1987 National Plan, the Retinal and Choroidal Diseases Panel did not find it necessary to evaluate separately this subprogram, whose priorities are reflected in research classified elsewhere in this program. Nevertheless, the panel chooses to reiterate the Plan's general recommendation to distribute postmortem human donor eyes for comparative study of various diseases and to use them to obtain correlations with premortem clinical findings. It also continues to be important to develop mechanisms for breeding promising animal models to provide adequate numbers for distribution to qualified investigators in retinal and choroidal diseases research.

REVISED SUBPROGRAM RESOURCE TABLE

RETINAL AND CHOROIDAL DISEASES

RELATED AREAS OF RESEARCH OPPORTUNITY AND NEED: TISSUE ACQUISITION AND DISTRIBUTION, HUMAN DONOR EYES AND ANIMAL MODELS (1-L1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Procure, prepare, and distribute postmortem human donor eyes affected with retinal and choroidal diseases; conduct ultrastructural, biochemical, and tissue culture studies; obtain correlations with premortem clinical findings. (D1)	SAME	0	0	0	0	0
2. Identify, develop, and maintain new animal models of retinal and choroidal diseases. (D2)	SAME	0	0	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	0	0	0 [0]	0 [0]
TOTAL FOR SUBPROGRAM		0 [0]	0	0	0 [0]	0 [0]
(% OF PROGRAM)		(0.0)	(0.0)	(0.0)	(0.0)	(0.0)

CORNEAL DISEASES

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Corneal Diseases Panel

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UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

CORNEAL DISEASES

Figures shown below are
Number of Projects [New Mechanisms]
(Percent of Projects in Program)
Dollars in Thousands

	FY 1981	Panel Rec. FY 1983	FY 1982	FY 1983	FY 1984	Applications FY 1983-84 Received	Funded	Percent
1. External Ocular Infections and Inflammatory Disease (2-E1)								
a. Herpes Simplex (2-E2)	21 (13.0) 2,153	28 (13.0) 2,996	21 [5] (12.9) 2,492	19 [3] (12.6) 2,508	23 [3] (15.1) 2,807	44	16	36.4
b. Herpes Zoster (2-E3)	0 (0.0) 0	2 (0.9) 214	0 [0] (0.0) 0	0 [0] (0.0) 0	0 [0] (0.0) 0	2	0	0.0
c. Adenovirus and Enterovirus (2-E4)	1 (0.6) 130	3 (1.4) 321	0 [0] (0.0) 0	1 [0] (0.7) 116	1 [0] (0.7) 126	2	1	50.0
d. Bacterial and Fungal Keratitis (2-E5)	9 (5.6) 702	12 (5.6) 1,284	8 [0] (4.9) 736	7 [0] (4.6) 769	8 [1] (5.3) 894	9	7	77.8
e. Chlamydial Keratoconjunctivitis (2-E6)	7 (4.3) 879	8 (3.7) 856	7 [0] (4.3) 917	7 [0] (4.6) 852	6 [0] (3.9) 994	10	4	40.0
f. Chronic Blepharitis (2-E7)	2 (1.2) 167	4 (1.9) 428	2 [0] (1.2) 205	3 [0] (2.0) 370	3 [0] (2.0) 404	1	1	99.9
g. Other Infections (2-E8)	2 (1.2) 289	2 (0.9) 214	2 [1] (1.2) 289	1 [0] (0.7) [illegible]	1 [1] (0.7) 234	8	2	25.0
SUBPROGRAM TOTAL	42 (25.9) 4,320	59 (27.4) 6,313	40 [6] (24.5) 4,639	38 [3] (25.2) 4,806	42 [5] (27.6) 5,459	76	31	40.8
2. Ocular Surface Problems (2-F1)								
a. Tear Film and Its Abnormalities (2-F2)	10 (6.2) 750	11 (5.1) 1,177	10 [0] (6.1) 796	9 [0] (6.0) 769	9 [1] (5.9) 957	13	7	53.8
b. Ocular Surface Disorders (2-F3)	30 (18.5) 3,021	35 (16.3) 3,745	30 [2] (18.4) 2,968	27 [3] (17.9) 3,133	26 [1] (17.1) 3,533	43	21	48.8

UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

CORNEAL DISEASES

Figures shown below are
Number of Projects [New Mechanisms]
(Percent of Projects in Program)
Dollars in Thousands

	FY 1981	Panel Rec. FY 1983	FY 1982	FY 1983	FY 1984	Applications FY 1983-84 Received	Applications FY 1983-84 Funded	Applications FY 1983-84 Percent
c. Drug Delivery and Toxicity (2-F4)	1 (0.6) 126	2 (0.9) 214	1 [1] (0.6) 130	1 [0] (0.7) 129	2 [2] (1.3) 370	5	4	80.0
SUBPROGRAM TOTAL	41 (25.3) 2,897	48 (22.3) 5,136	41 [3] (25.2) 3,894	37 [3] (24.5) 4,031	37 [4] (24.3) 4,860	61	32	52.5
3. Refractive Problems and Contact Lenses (2-G1)	19 (11.7) 1,682	26 (12.1) 2,782	20 [3] (12.3) 1,875	16 [1] (10.6) 1,707	16 [1] (10.5) 2,143	28	5	17.9
4. Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Disease (2-H1)								
a. Endothelial Tissue Culture, Replacement and Repair (2-H2)	5 (3.1) 585	7 (3.3) 749	5 [0] (3.1) 745	7 [2] (4.6) 1,051	6 [1] (3.9) 597	13	6	46.2
b. In Vivo Evaluation of Corneal Epithelial and Endothelial Membrane Function (2-H3)	3 (1.9) 259	5 (2.3) 535	2 [0] (1.2) 214	2 [1] (1.3) 263	2 [0] (1.3) 281	4	1	25.0
c. In Vivo Morphologic Evaluation--Specular Microscopy (2-H4)	2 (1.2) 238	3 (1.4) 321	2 [0] (1.2) 317	1 [0] (0.7) 149	1 [0] (0.7) 164	0	0	0.0
d. Endothelial and Epithelial Transport Processes (Corneal Hydration and Edema) (2-H5)	10 (6.2) 1,193	13 (6.0) 1,391	11 [2] (6.7) 1,467	16 [0] (10.6) 2,175	16 [0] (10.5) 2,106	16	12	75.0
e. Stromal Swelling and Transparency (2-H6)	7 (4.3) 570	8 (3.7) 856	6 [0] (3.7) 600	5 [0] (3.3) 597	5 [0] (3.3) 522	8	1	12.5
f. Normal Corneal Development (2-H7)	2 (1.2) 181	2 (0.9) 214	4 [0] (2.5) 411	4 [0] (2.6) 558	2 [0] (1.3) 534	5	2	40.0
g. Corneal Dystrophies, Inherited Disorders, and Developmental Anomalies (2-H8)	4 (2.5) 485	7 (3.3) 749	4 [0] (2.5) 452	3 [0] (2.0) 409	2 [0] (1.3) 284	1	0	0.0

UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

CORNEAL DISEASES

Figures shown below are
Number of Projects [New Mechanisms]
(Percent of Projects in Program)
Dollars in Thousands

	FY 1981	Panel Rec. FY 1983	FY 1982	FY 1983	FY 1984	Applications FY 1983-84 Received	Funded	Percent
SUBPROGRAM TOTAL	33 (20.4) 3,514	45 (20.9) 4,815	34 [2] (20.9) 4,206	38 [3] (25.2) 5,202	34 [1] (22.4) 4,488	47	22	46.8
5. Corneal Transplantation and Stromal Wound Healing (2-J1)								
a. Inflammation and Repair (2-J2)	16 (9.9) 1,256	20 (9.3) 2,140	16 [0] (9.8) 1,421	13 [0] (8.6) 1,742	14 [0] (9.2) 1,773	19	7	36.8
b. Corneal Transplantation (2-J3)	11 (6.8) 1,180	17 (7.9) 1,819	12 [1] (7.4) 1,319	9 [0] (6.0) 947	9 [1] (5.9) 1,172	14	4	28.6
SUBPROGRAM TOTAL	27 (16.7) 2,436	37 (17.2) 3,959	28 [1] (17.2) 2,740	22 [0] (14.6) 2,689	23 [1] (15.1) 2,945	33	11	33.3
PROGRAM TOTAL	162 (100.0) 15,849	215 (100.0) 23,005	163 [15] (100.0) 17,354	151 [10] (100.0) 18,435	152 [12] (100.0) 19,895	245	101	41.2

REVISED PROGRAM RESOURCE TABLE

CORNEAL DISEASES

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
		Research Grants	Clinical Trials		
1. External Ocular Infections and Inflammatory Disease (2-E1)					
a. Herpes Simplex (2-E2)	23 [3] (14.9) 2,807	33 (15.3)	0 (0.0)	24 [0] (14.5) 2,875	21 [0] (12.2) 3,003
b. Herpes Zoster (2-E3)	0 [0] (0.0) 0	3 (1.4)	0 (0.0)	0 [0] (.0) 0	1 [0] (.6) 181
c. Adenovirus and Enterovirus (2-E4)	1 [0] (0.6) 126	4 (1.9)	0 (0.0)	1 [0] (.6) 138	1 [0] (.6) 150
d. Bacterial, Fungal, Amoebic, and Parasitic Keratitis (2-E5)	9 [2] (5.8) 1,128	17 (7.9)	0 (0.0)	8 [2] (4.8) 1,229	9 [0] (5.2) 1,204
e. Chlamydial Keratoconjunctivitis (2-E6)	6 [0] (3.9) 994	7 (3.2)	1 (5.0)	5 [0] (3.0) 1,138	5 [0] (2.9) 1,221
f. Chronic Blepharitis (2-E7)	3 [0] (1.9) 404	4 (1.9)	0 (0.0)	3 [0] (1.8) 519	2 [0] (1.2) 283
SUBPROGRAM TOTAL	42 [5] (27.3) 5,459	68 (31.5)	1 (5.0)	41 [2] (24.7) 5,899	39 [0] (22.7) 6,042
2. Ocular Surface Problems (2-F1)					
a. Tear Film and Its Abnormalities (2-F2)	9 [1] (5.8) 956	17 (7.9)	0 (0.0)	8 [2] (4.8) 953	10 [1] (5.8) 1,097
b. Ocular Surface Disorders (2-F3)	27 [1] (17.5) 3,678	34 (15.7)	0 (0.0)	30 [1] (18.1) 4,694	28 [3] (16.3) 4,125

REVISED PROGRAM RESOURCE TABLE

CORNEAL DISEASES

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
c. Drug Delivery and Toxicity (2-F4)	2 [2] (1.3) 370	4 (1.9)	0 (0.0)	3 [1] (1.8) 573	5 [0] (2.9) 741
SUBPROGRAM TOTAL	38 [4] (24.7) 5,004	55 (25.5)	0 (0.0)	41 [4] (24.7). 6,220	43 [4] (25.0) 5,963
3. Correction of Refractive errors (2-G1)	16 [1] (10.4) 2,141	14 (6.5)	10 (50.0)	16 [3] (9.6) 1,635	16 [3] (9.3) 1,893
4. Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Disease (2-H1)					
a. Endothelial Tissue Culture, Replacement and Repair (2-H2)	6 [1] (3.9) 597	8 (3.7)	0 (0.0)	7 [1] (4.2) 1,104	7 [2] (4.1) 1,250
b. In Vivo Evaluation of Corneal Epithelial and Endothelial Membrane Function (2-H3)	3 [0] (1.9) 445	5 (2.3)	0 (0.0)	7 [0] (4.2) 1,273	6 [1] (3.5) 1,132
c. Endothelial and Epithelial Transport Processes (Corneal Hydration and Edema) (2-H5)	15 [0] (9.7) 1,960	20 (9.3)	0 (0.0)	14 [0] (8.4) 1,776	16 [1] (9.3) 2,040
d. Stromal Swelling and Transparency (2-H6)	5 [0] (3.2) 522	7 (3.2)	0 (0.0)	6 [0] (3.6) 1,140	6 [1] (3.5) 1,034
e. Normal Corneal Development (2-H7)	4 [0] (2.6) 534	8 (3.7)	0 (0.0)	2 [0] (1.2) 340	3 [0] (1.7) 491
f. Corneal Dystrophies, Inherited Disorders, and Developmental Anomalies (2-H8)	2 [0] (1.3) 284	4 (1.9)	0 (0.0)	1 [1] (.6) 298	1 [0] (.6) 292
SUBPROGRAM TOTAL	35 [1] (22.7) 4,342	52 (24.1)	0 (0.0)	37 [2] (22.3) 5,931	39 [5] (22.7) 6,239

REVISED PROGRAM RESOURCE TABLE

CORNEAL DISEASES

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
5. Corneal Transplantation and Stromal Wound Healing (2-J1)					
a. Inflammation and Repair (2-J2)	14 [0] (9.1) 1,774	17 (7.9)	0 (0.0)	13 [1] (7.8) 1,805	16 [0] (9.3) 1.980
b. Corneal Transplantation (2-J3)	9 [1] (5.8) 1,172	10 (4.6)	9 (45.0)	18 [1] (10.8) 2,548	19 [1] (11.0) 2,746
SUBPROGRAM TOTAL	23 [1] (14.9) 2,946	27 (12.5)	9 (45.0)	31 [2] (18.7) 4,353	35 [1] (20.3) 4,726
PROGRAM TOTAL	154 [12] (100.0) 19,392	216 (100.0)	20 (100.0)	166 [13] (100.0) 24,038	172 [13] (100.0) 24,863

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External Ocular Infections and Inflammatory Diseases

1

Herpes Simplex

Perspective on Recent Research

Herpes simplex virus (HSV) is the most common cause of infectious blindness in the United States; approximately 500,000 cases are reported annually.[1,2] In man, ocular HSV-1 infection results in spread of the virus from sites of infection along sensory nerves to the trigeminal ganglion and central nervous system (CNS). Once in the trigeminal ganglion, HSV-1 can remain associated with neurons in a latent nonreplicative form where it does little damage to the host. However, in many individuals HSV-1 can be periodically reactivated from its latent form within the trigeminal ganglion and spread back along sensory nerves to cause recurrent ocular infections. Thus, corneal damage caused by ocular HSV-1 infection is usually the result of a viral-induced inflammatory response which originates in an individual's trigeminal ganglion and then spreads to the cornea along sensory nerves.

Unfortunately, very little is known about how HSV establishes latency, maintains latency, and is reactivated to cause ocular disease. For these reasons, two major objectives in this subprogram as outlined in the Plan were to investigate mechanisms of herpetic neuronal latency and to develop more effective, specific, and safe topical and systemic drugs to prevent recurrent HSV infections of the eye.

Developments in recombinant DNA technology that have occurred since the Plan was written have made it possible to isolate individual genes from the HSV chromosome and study how they are regulated during virus replication.[3-6] In addition, genes for the major viral antigens expressed on the surface of corneal cells during ocular herpes infection have been cloned and expressed in both prokaryotic and eukaryotic expression vectors.[7-10] These recent developments in the molecular biology of HSV have opened up new opportunities by which the pathogenesis and latency of HSV-1 can be investigated at a molecular level and by which new multivalent vaccines can be developed to potentially provide lifelong protection against HSV infection. It is these exciting new areas of HSV research upon which this report on herpes simplex will focus.

Progress in Areas Discussed in the 1983-1987 Plan

As pointed out in the Plan, ocular damage caused by herpes infection is largely the result of its chronic recurrent pattern. With each attack, more permanent damage may occur. An important discovery with far-reaching implications is that latent herpetic reservoirs, which are the source of recurrent HSV infections, exist in deep-seated neuronal tissues.[11-13] Vision scientists have developed an in vivo experimental system for reactivating latent HSV infections from neural tissue, making it possible to study the process by which latent HSV infection becomes reactivated.[14,15]

However, the specific HSV genes involved in the pathogenesis of ocular HSV infection and the virus-specific genes involved in the establishment, maintenance, and reactivation of virus from latency have not been identified. It is in this area of study that recent advances in the molecular genetics of viral pathogenesis have been applied to investigations of the molecular basis of HSV pathogenesis and latency. For example, investigators have used intratypic recombinants of HSV-1 to study the genetic basis of virus replication within corneal tissues. They found that incorporation of a segment of DNA [map unit .7-.83] from an invasive stromal disease-producing HSV-1 strain into the genome of a noninvasive epithelial disease-producing HSV-1 strain resulted in a recombinant with characteristics of the donor stromal disease-producing virus.[16]

Intertypic recombinants have also been used to investigate the genetic basis of virus spread within tissues of the CNS. Recently, a specific region of the HSV-1 genome was shown to be responsible for a 10 million-fold increase in the ability of this virus to spread within the CNS of infected mice.[17,18]

New and Developing Areas of Research

In 1983, the Plan anticipated that recombinant DNA technology would permit genetic manipulation of the HSV chromosome such that an antigenically pure and safe vaccine could be developed. Such a vaccination could be given early in life, before establishment of the latency which follows natural exposure to HSV. Since publication of the Plan, there have been rapid advances in the application of recombinant DNA technology to herpesvirus research. For example, this technology has led to the isolation of genes that code for the major glycoprotein (glycoprotein D) of HSV.[7-9] In many cases, it has been found that cloned HSV specific genes can be transcribed in either bacteria or tissue culture cells, which result in the synthesis of HSV specific glycoproteins.[7,10] More importantly, it has been shown that HSV glycoproteins synthesized from recombinant DNA molecules can elicit protective immunity in laboratory animals following a lethal challenge with live HSV.[7,10] Because HSV-specific glycoproteins are the antigens which the host's immune response recognizes during ocular HSV infection, these developments could make it possible to develop virus-free vaccines against ocular herpesvirus infections.

Rapid progress has also been made in the last two to three years in applying recombinant DNA technology to the mapping of genes involved in directing the transcription and replication of the HSV genome.[3-6] However, our knowledge about how these genes and their protein products direct the spread of HSV-1 from sites of infection into the trigeminal ganglia and brain remains scant. Future application of recombinant DNA methodology to the study of the pathogenesis of ocular HSV infection could lead to the identification of HSV specific sequences responsible for the spread of HSV-1 from the cornea to the trigeminal ganglia, and ultimately, the identification of the viral genes responsible for the establishment and maintenance of HSV within the trigeminal ganglia during latent infections. In addition, regulation of prokaryotic gene expression by genetic engineering is already a reality. HSV has been found to contain regulatory sequences upstream from a number of genes encoding virus specific polypeptides.[3-6] This raises the possibility of applying techniques of molecular biology to interfere with the expression of HSV specific genes found to be involved in the reactivation of HSV from its inactivated state within neurons. This could possibly provide a mechanism to interfere with the expression of latent HSV genomes within neurons, thereby preventing reactivation of the virus and its spread along sensory nerves to the cornea.

Balance of Effort Within Subprogram

In FY 1984, the National Eye Institute funded a total of 23 grants for research on external ocular infections and inflammatory diseases caused by herpes simplex virus. Three additional small grants were funded in this area. The largest percentages of funding in this subprogram were in Program Development Priority D1, to characterize infectious and immune factors in defined forms of herpes and to develop better diagnostic techniques, and Priority D3, to develop specific antiviral drugs for keratouveitis and for preventing recurrent disease.

Less funding was made available, as the Plan called for, for studies in the Program Base to define the roles of live herpes simplex, herpetic antigen, and antigenically altered corneal cell membranes in corneal disease (B1) and to modify host response via anti-inflammatory and immunopotentiating agents (B2). Only three grants were funded in Priority D2 to determine neuronal and viral factors in herpetic latency and triggers for reactivation and shedding, three fewer than in FY 1981 and five fewer than called for by the Plan. One grant was funded to use attenuated herpetic strains in vaccines and one to use monoclonal antibodies and/or programmed lymphocytes to manipulate herpetic responses in fulfillment of some aspects of Priorities D4 and D5. One grant was funded in FY 1984 to use monoclonal antibody, programmed lymphocyte, and recombinant DNA techniques to manipulate the herpetic immune response.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Panel believes that the two Program Base Categories continue to be relevant and should be maintained for the balance of the current five-year period of the Plan. In the Panel's judgement, because the number of grants funded in Program Development Priority D3 in FY 1984 matches what the Plan called for, this category should now be considered part of the Program Base.

Further research on the infectious and immune factors in defined forms of herpes, development of better diagnostic techniques and determination of factors predictive of the clinical course of the disease following appropriate therapy, and determination of the neuronal and viral factors in herpetic latency and the mechanisms that trigger viral reactivation and shedding are critical to understanding inflammation caused by ocular herpes. This is especially true for studies evaluating neuronal and viral factors responsible for herpetic latency (D2) The low level of funding in this area is in part due to the lack of good animal models for study of viral reactivation and recurrent eye disease. Nevertheless, the Panel believes that this Program Development Priority needs to be reemphasized at the recommended 1983 level because of the importance of HSV latency to ocular disease.

Rapid progress has continued to be made in the application of monoclonal antibodies and cloned T-cells to investigate the pathogenesis of herpesvirus induced diseases.[18-21] These areas of ongoing research offer particular opportunities for increasing knowledge about how individuals resist ocular HSV infection. This information is important in the design of antiviral vaccines and antiviral agents and for the development of strategies for immunotherapy of ocular herpetic disease. Thus, the Panel recommends increasing the number of projects in this area (D4) to two grants in FY 1987.

Recommended Changes in Program Base and/or Program Development Priorities

Due to rapid progress in the application of recombinant DNA technology to herpesvirus research, there is a great likelihood that application of molecular genetics to study the pathogenesis of ocular HSV-1 infection could lead to the identification of HSV-1-specific DNA sequences responsible for the spread of HSV-1 from the cornea to the trigeminal ganglia—and ultimately the viral genes responsible for the establishment and maintenance of HSV-1 within the trigeminal ganglia during latent infection—and for the reactivation of HSV during recrudescence. Therefore, the Panel recommends the addition of a Program Development Priority (D5) to isolate the genes involved in the pathogenesis of ocular HSV-1 infection and to design strategies to manipulate the expression of those viral specific genes involved in the virulence and latency of HSV.

Isolation and characterization of individual genes of the HSV genome have become possible in recent years by the application of recombinant DNA technology to herpesvirus research. Because HSV genetic material can remain latent in sensory and autonomic peripheral ganglia of humans, development of a virus-free vaccine that could elicit protective immunity against ocular HSV-1 infection would provide an important advantage over attenuated or inactivated virus vaccines. Application of recombinant DNA technology to the control of ocular HSV-induced diseases could lead to the development of these vaccines. Therefore, the Panel recommends the addition of a sixth Program Development Priority (D6) to produce antigens that elicit immunity against HSV by recombinant DNA technology and study their use in preventing primary and recrudescent HSV-1 infections.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: HERPES SIMPLEX (2-E2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Define roles of live herpes simplex, herpetic antigen, and antigenically altered corneal cell membranes in corneal disease. (B1)	3	3	3 [1]	3 [1]	3	4	1	25.0
2. Modify host response via anti-inflammatory and immunopotentiating agents. (B2)	3	3	3	2	2	6	2	33.3
TOTAL FOR PROGRAM BASE	6	6	6 [1]	5 [1]	5 [0]	10	3	30.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Characterize infectious and immune factors in defined forms of herpes and develop better diagnostic techniques. (D1)	4	5	4	4	6 [1]	12	4	33.3
2. Determine neuronal and viral factors in herpetic latency and triggers for reactivation and shedding. (D2)	6	8	5 [1]	4 [2]	3	8	2	25.0
3. Develop specific antiviral drugs for keratouveitis and for preventing recurrent disease. (D3)	5	7	6	6	7 [1]	6	4	66.7
4. Use attenuated herpetic strains in vaccines. (D4)	0	1	0 [2]	0	1	3	1	33.3
5. Use monoclonal antibodies, programmed lymphocytes, and recombinant DNA techniques to manipulate herpetic response. (D5)	0	1	0 [1]	0	1 [1]	5	2	40.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	15	22	15 [4]	14 [2]	18 [3]	34	13	38.2
TOTAL FOR SUBPROGRAM	21	28	21 [5]	19 [3]	23 [3]	44	16	36.4
(% OF PROGRAM)	(12.9)	(13.0)	(12.9)	(12.6)	(15.1)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: HERPES SIMPLEX (2-E2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Define roles of live herpes simplex, herpetic antigen, and antigenically altered corneal cell membranes in corneal disease. (B1)	SAME	3	3	0	1	0
2. Modify host response via anti-inflammatory and immunopotentiating agents. (B2)	SAME	2	3	0	2	2
3. Develop specific antiviral drugs for keratouveitis and for preventing recurrent disease. (B3)	MOVED (WAS D3)	7 [1]	7	0	6	2
TOTAL FOR PROGRAM BASE		12 [1]	13	0	9 [0]	4 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Characterize infectious and immune factors in defined forms of herpes and develop better diagnostic techniques. (D1)	SAME	6 [1]	6	0	7	8
2. Determine neuronal and viral factors in herpetic latency and triggers for reactivation and shedding. (D2)	SAME	3	6	0	4	3
3. Use attenuated herpetic strains in vaccines. (D3)	SAME (WAS D4)	1	2	0	2	3
4. Use monoclonal antibodies, programmed lymphocytes, and recombinant DNA techniques to manipulate herpetic response. (D4)	SAME (WAS D5)	1 [1]	3	0	2	3
5. Isolate the genes involved in the pathogenesis of ocular HSV-1 infection and design strategies to manipulate the expression of those viral-specific genes involved in the virulence and latency of HSV. (D5)	NEW	0	2	0	0	0
6. Produce antigens that elicit immunity against HSV by recombinant DNA technology and study their use preventing primary and recrudescent HSV-1 infections. (D6)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		11 [2]	20	0	15 [0]	17 [0]
TOTAL FOR SUBPROGRAM		23 [3]	33	0	24 [0]	21 [0]
(% OF PROGRAM)		(14.9)	(15.2)	(0.0)	(14.4)	(12.2)

Herpes Zoster

Perspective on Recent Research

The Plan states that understanding the pathogenesis and host responses to varicella-zoster virus (VZV), the agent that causes ophthalmic herpes zoster, would be of enormous benefit to neurologists, internists, pediatricians, immunologists, and oncologists involved in treating individuals with this disease. To increase knowledge about the pathogenesis of acute and chronic zoster, an animal model is desperately needed.

Techniques of recombinant DNA technology are just now beginning to be applied to herpes zoster research.[1] Using this new technology, it may soon be possible to develop and test virus-free vaccines for this disease. An animal model for ophthalmic zoster would also be extremely valuable in evaluating new vaccines developed through the application of recombinant DNA technology. Since the Plan was published, there have been some successes in the development of animal models for varicella-zoster virus infections[2,3] and this report will focus on this topic.

Progress in Areas Discussed in the 1983-1987 Plan

Recently it has been reported that weanling guinea pigs are susceptible to infection with varicella zoster virus cultured in embryonic guinea pig tissue.[2] VZV infection in the guinea pigs was documented by the appearance of antibody in inoculated animals and by transmission of the disease from infected guinea pigs to their uninoculated cage mates. However, the clinical course of the disease was not similar to human VZV infections because cutaneous lesions did not appear on the guinea pigs and the pathogenesis of the disease was different from that in humans.

An alternative approach to the study of VZV infections, therefore, would be to find a non-human varicella-like virus which would cause a clinical disease in animals similar to VZV infections in humans. Such a virus has been found in primates. Several varicella-like viruses have been isolated from monkeys in which they cause a disease similar to varicella in humans.[4-6] All of these isolates cross-react with human VZV by neutralization and complement fixation tests.[7,8] This suggests that the human and primate varicella viruses are phylogenetically related.

Recently, it has been found that human VZV DNA also shares considerable DNA homology with the DNA of simian varicella-zoster-like viruses.[3] This suggests that information gained from studies on the pathogenesis and antiviral therapy of simian varicella virus infections of non-human primates can be extrapolated to human VZV infections of the eye.

New and Developing Areas of Research

Applications of recombinant DNA technology to VZV research has resulted in the identification of the DNA sequences coding for a major glycoprotein of VZV.[1] Continued application of recombinant DNA technology to the study of VZV infections will provide new opportunities for the development of a virus-free vaccine to provide immunity against herpes zoster.

Balance of Effort Within Subprogram

In FY 1984, there were no projects funded to develop animal models for herpes zoster or to develop and evaluate antiviral and anti-inflammatory therapy for ophthalmic zoster. The lack of activity in this area probably reflects the difficulty in working with VZV and the lack of a reliable animal model to investigate problems in VZV pathogenesis, immunology, and antiviral therapy.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

In 1983, the Panel recommended that one project be funded to develop a satisfactory animal model for the evaluation of zoster infections of the eye and one project to develop and evaluate antiviral and anti-inflammatory therapy for use in acute ophthalmic zoster. The Panel continues to believe that there is a need for research in these areas; therefore, they warrant NEI support over the next two years at the levels recommended in the Plan. A "Request for Applications" may be an appropriate mechanism to stimulate activity in herpes zoster research.

Recommended Changes in Program Base and/or Program Development Priorities

Attenuated live VZV strains have been developed as a vaccine against varicella infections.[9,10] Because human VZV and simian varicella virus (SVV) are genetically related and express many of the same antigens in infected cells[3,7,8], the development of an ocular zoster model utilizing SVV and non-human primates would provide an opportunity to test human VZV vaccines, anti-inflammatory agents, and antiviral drugs for their effectiveness against VZV infections of the eye. Therefore, the Panel recommends changing the first Program Development Priority (DI) to read: "Develop an animal model for herpes zoster infection; test new treatments in animal models and explore the use of simian varicella virus in an animal model for human varicella zoster infection of the eye."

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: HERPES ZOSTER (2-E3)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1 Develop animal model for herpes zoster; test new treatments. (D1)	0	1	0	0	0	1	0	
2. Develop and evaluate antiviral and anti-inflammatory therapy for ophthalmic zoster. (D2)	0	1	0	0	0	1	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	0	2	0 [0]	0 [0]	0 [0]	2	0	0.0
TOTAL FOR SUBPROGRAM	0	2	0 [0]	0 [0]	0 [0]	2	0	0.0
(% OF PROGRAM)	(0.0)	(0.9)	(0.0)	(0.0)	(0.0)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: HERPES ZOSTER (2-E3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop an animal model for herpes zoster; test new treatments in animal models and explore the use of simian varicella virus infection as an animal model for human varicella zoster infection of the eye. (D1)	EXPANDED	0	2	0	0	1
2. Develop and evaluate antiviral and anti-inflammatory therapy for ophthalmic zoster. (D2)	SAME	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	3	0	0 [0]	1 [0]
TOTAL FOR SUBPROGRAM		0 [0]	3	0	0 [0]	1 [0]
(% OF PROGRAM)		(0.0)	(1.4)	(0.0)	(0.0)	(0.6)

Adenovirus and Other Viruses

Perspective on Recent Research

This section was previously entitled "Adenovirus and Enterovirus". The Plan recognizes the morbidity associated with epidemics of adenovirus keratoconjunctivitis plus recent observations that adenovirus type 12 produces cancer in laboratory animals and enterovirus causes epidemics of hemorrhagic conjunctivitis throughout the world. Since the publication of the Plan, the epidemic of acquired immunodeficiency syndrome (AIDS) has been recognized and the causative virus, HTLV-III/LAV, [now referred to as human immunodeficiency virus (HIV)] isolated.[1,2] Many AIDS patients have ocular involvements.[3-5] The possibility of transmitting HIV in ocular secretions and/or donor corneas has been raised. The eye provides a unique site to study the pathogenesis of AIDS and possibly to study its transmission. In contrast, there have been no significant research developments regarding ocular adenovirus or enterovirus infections.

Progress in Areas Discussed in the 1983-1987 Plan

Adenovirus grows slowly in tissue culture. Researchers have developed better reagents, especially specific polyclonal and monoclonal antibodies as well as better techniques to identify adenoviral antigens on scrapings from the ocular surface and from cultures. These technical advances have improved the rapidity and sensitivity of diagnosis.

However, there is still a lack of effective agents for the prevention of adenoviral infections or the lessening of ocular sequelae. Likewise, a reliable animal model has not been developed. Thus, the Program Development Priorities have not yet been attained.

New and Developing Areas of Research

The recognition of AIDS as a new infectious disease has been accompanied by major breakthroughs and new research opportunities. Most of the severe clinical syndromes have been identified, the immunological defects characterized, the etiologic agent, HIV, isolated,[1,2] and several screening techniques for identifying HIV antigen developed.[6] So far, most of the ocular involvements appear to be sequelae of opportunistic secondary infections, especially cytomegalovirus infections.[3-5] The HIV virus can be transmitted in various body fluids including blood and blood products,[6,7] and semen[8] and possibly saliva.[9] The HIV virus has also been isolated from human tears[10] and conjunctiva[11] and HIV antigens have been identified in the corneal[12] and conjunctival[11] epithelium. Such observations suggest the possibility of the transmission of AIDS through an ocular route,[13,14] but to date there have been no reports documenting the transmission of AIDS by tears or donor corneal tissue. Although it is generally believed that the risk of transmission of AIDS via tears or by way of contaminated tonometers or contact lenses is unlikely, specific recommendations for preventing the possible transmission of HIV in tears have been made by the Center for Disease Control.[13] Because HIV antigens have been identified in corneal tissue, the Eye Bank Association of America currently requires blood serum tests for HIV antibody of all eye donors and prohibits the use of "corneas for transplant from donors in known or suspected high risk groups for AIDS, regardless of blood serum results."[15]

Balance of Effort Within Subprogram

In FY 1984 one of three adenovirus research grants recommended by the Plan for FY 1983 was funded. Because there have been essentially no new developments in this area, this seems appropriate. However, the extension of the section to include "other viruses" and the major new developments associated with AIDS open many new potential areas of research. Because most AIDS research is taking place in viral disease research laboratories, it is unlikely that specific eye-related issues will be addressed in these settings.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

Currently there is no Program Base in this area because there is little research underway in this field. However, new knowledge in AIDS makes it feasible to expand this area and to develop new Program Development Priorities. Especially important research areas are those dealing with viral possible transmissibility via tears, corneal and conjunctival tissue, and ophthalmic instruments. Because there is no known cure for the disease, emphasis should be given to prevention.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends the Program Development Priority category D1 be retained and that D2 be expanded to include all viruses. A third category should be added for research on AIDS.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: ADENOVIRUS AND OTHER VIRUSES (2-E4)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop animal model of adenoviral infection. (D1)	1	2	0	1	1	2	1	50.0
2. Evaluate new antiviral and anti-inflammatory agent in adenoviral infection. (D2)	0	1	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	3	0 [0]	1 [0]	1 [0]	2	1	50.0
TOTAL FOR SUBPROGRAM	1	3	0 [0]	1 [0]	1 [0]	2	1	50.0
(% OF PROGRAM)	(0.6)	(1.4)	(0.0)	(0.7)	(0.7)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: ADENOVIRUS AND OTHER VIRUSES (2-E4)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop animal model of adenoviral infection. (D1)	SAME	1	2	0	1	1
2. Evaluate new antiviral and anti-inflammatory agents for therapy of ocular infections due to adenoviruses and other viruses. (D2)	EXPANDED, LESS SPECIFIC	0	1	0	0	0
3. Evaluate potential contribution of ocular secretions to spread of AIDS. (D3)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		1 [0]	4	0	1 [0]	1 [0]
TOTAL FOR SUBPROGRAM		1 [0]	4	0	1 [0]	1 [0]
(% OF PROGRAM)		(0.6)	(1.8)	(0.0)	(0.6)	(0.6)

Bacterial, Fungal, Amoebic, and Parasitic Keratitis

Perspective on Recent Research

Nonviral infectious disease of the cornea continues to be a significant problem in the United States. The increased use of extended wear contact lenses has been associated with an additional number of reports of infection of the cornea, making this type of keratitis an increasingly important problem.[1]

In southern latitudes the incidence of fungal infection continues to be relatively high, with *Fusarium solani* remaining the most frequent cause. Chronic use of topical corticosteroids and systemic immunosuppression facilitates infection by yeasts such as *Candida* and other opportunistic fungi such as *Aspergillus* and *Curvularia*.

Recently, a number of reports have characterized the infection caused by *Acanthomoeba* (a topic not discussed in the Plan), detailing its chronic course and resistance to treatment.[2,3] Laboratory investigation of this amoeba has been hampered by the cumbersome and unreliable methods available for its culture and identification. The serotyping of this organism has been inexact, with discrepancies between laboratories and even between samples not uncommon. Recently, a clinical report in the British literature claims clinical cure of this infection by the use of diethylpropamide.[4] Laboratory investigation of sensitivity of the organism to this agent and a variety of antifungal agents have not yet been published.

Greater progress has been reported in research on onchocerciasis and ocular leprosy, neither of which were discussed in the Plan. Onchocerciasis remains a major public health problem in large parts of Africa and Central and South America. Work has been progressing on developing an animal model for the disease as well as on growing the parasite in tissue and cell-free environments.[5]

Ocular leprosy continues to be a risk for large segments of the world's population, particularly in developing nations. Recent advances in the study of this disease have come from the development of an animal model in the armadillo.[6] Treatment continues to be long-term, and resistance to treatment still occurs.

Progress in Areas Discussed in 1983-87 Plan

The basis for bacterial infection of the cornea has been examined in electron microscopic studies of the corneal epithelium. It has been found that bacterial adhesion to epithelial cells is the initial event in infection.[7] The particular susceptibility of keratinized cells to bacterial infection has been noted in experimental vitamin A deficiency; however, the relative noninfectivity of these cells by virus has also been noted.[8] The role of polymorphonuclear leukocytes in causing stromal ulceration in bacterial infection has been characterized[9] as well as the direct tissue-destructive toxin released by *Pseudomonas* strains.[10]

New antibiotics continue to be introduced for the treatment of bacterial keratitis, and newer antifungal medications are the subject of experimental clinical trials.[11]

New and Developing Areas of Research

The quantitation of corneal stromal involvement by infectious processes has been approached by determining the area of stromal infiltration using digital-image processing technology.[12] The clinical resolution of the disease has been correlated with the disappearance of the infective agent. Clinical use of this technology may be useful in evaluating the response to therapy. The general abandonment of subconjunctival delivery of antibiotics in favor of more frequent use of topical medications has improved the ease of treating of bacterial keratitis without compromising effectiveness. Further work should be done to determine the optimal frequency of antibiotic dosage for infectious keratitis.

As noted above, no studies of onchocercarial-related corneal diseases, ocular leprosy, or amoebic keratitis were recommended in the Plan. However, because of the extremely high worldwide prevalence of these disorders and the existence of several research needs and opportunities relating to them, the Panel believes that the Plan should be amended to recognize ongoing NEI support of research in these fields and to suggest possibilities for future program development in these areas.

Onchocerciasis. The causative agent of onchocerciasis is *Onchocerca volvulus,* a filarial worm that lives in the subcutaneous tissues of the body. Major endemic regions of the world include large parts of Africa and portions of Central and South America. In Africa alone, *0. volvulus* is thought to infect over 20 million inhabitants, and in many villages onchocerciasis may afflict upwards of 50 percent of the adult population. An estimated 1.5 to 2 million people worldwide are blind from from this disease.[13]

Female worms living in subcutaneous tissues produce larval forms known as microfilariae, which are responsible for almost all of the pathology associated with this infection. Microfilariae migrate throughout subcutaneous tissues where they cause considerable discomfort due to the development of skin lesions such as pruritic rash. In heavily infected individuals microfilariae may invade the eye via the conjunctiva, the vasculature, or possibly via the optic nerve where they can often be seen in copious numbers swimming in the aqueous humor. Once in the cornea, *O. volvulus* produces two forms of corneal disease—punctate keratitis (also known as "snowflake opacities") and sclerosing keratitis.[14,15]

Punctate keratitis is caused by an inflammatory response to degenerating microfilariae within the cornea. These lesions usually disappear within several weeks, leaving no permanent damage. Sclerosing keratitis, on the other hand, is a chronic response to the parasite and can result in corneal opacity and blindness. The pathology of sclerosing keratitis involves marked proliferation of blood vessels and the deposition of scar tissue within the cornea.

Pharmacologic intervention in onchocerciasis, with either diethylcarbamazine (DEC) or suramin, results in effective mass killing of microfilariae. Unfortunately, the rapid death and disintegration of so many microfilariae within the cornea elicits a painful pruritis and an eosinophil-rich inflammatory response that is sometimes considered to be worse than the disease itself (the so-called Mazzotti reaction). This reaction suggests that so long as the parasites remain viable, the host-parasite relationship is delicately balanced and little or no response to migrating microfilariae occurs. However, once microfilariae are dead, the host mounts an immune response against the parasite.

The results of recent research suggest that several opportunities now exist for studies that could lead to a successful understanding of ocular onchocerciasis.[5]

First, an attempt at defining an animal model using cynomolgus monkeys injected with microfilariae of a closely related species, *O. lienalis*, appears somewhat promising.[16] Second, recent preliminary studies have suggested a link between the release of defined eosinophil-derived products and the development of the Mazzotti reaction in skin biopsies of onchocerciasis patients undergoing treatment with DEC.[17] Third, a comparison of a new class of drug, the ivermectins, with DEC suggests that it may be as effective a microfilariacide as DEC without causing an intense pruritis and eosinophil reaction.[18] Lastly, work with another filariid, *Brugia pahangi*, has offered the prospect that it may be possible to maintain long-term, viable adult filariids in cell-free culture systems in which viable microfilariae are produced. In the absence of a developed animal model, this would offer the next best hope of deriving onchocercal materials for antigen preparations and for drug screening studies.[19]

In the absence of a well-characterized animal model of ocular onchocerciasis, it is essential to elaborate the immunopathological mechanisms that underlie the pathology observed in this infection. Thus, studies that probe the cellular and humoral processes underlying host responses to microfilariae in the skin and the eye, in particular, are clearly needed. In addition, good epidemiological studies that can document the amount of morbidity in endemic areas may offer insight in differences in host responses that can be exploited for potential gain against the disease process.

Ocular Leprosy. The causative agent in leprosy is *Mycobacterium leprae*. As many as 16 million people worldwide are affected with this disease, and as many as 4 million people may suffer the ocular consequences of this infection. The disease is found in parts of South America, Africa, and Asia, and represents one of the leading causes of blindness worldwide. No known nonhuman reservoir for this infectious agent has been found.

Any organ of the body can be affected by this bacillus, but the ophthalmologist is concerned with the consequences of the involvement of the facial and trigeminal nerves as well as uveal involvement. The clinical manifestations of the ocular disease are iridocyclitis, due to direct uveal involvement with the organism. The cornea and external disease consequences of infection may all relate to involvement of the trigeminal and facial nerves which results in lagophthalmos, exposure keratitis, and neurokeratitis.

Recently, an experimental model has been developed in the nine-banded armadillo. This experimental model allows study of the ocular infection.[5]

Research needs to be directed toward the development of a treatment. Dapsone (diaminodiphenylsulphone) is the best available therapy, but resistant strains of the leprosy organism have appeared. In addition, this therapy requires many years and is not always successful.

Immunological investigations have provided no simple explanation for the existence of this mycobacterium in patients. Possibly the organism exists because of an abnormality in immunological control mechanisms, and the relationship between the bacillus and the immunological control should be pursued.

Amoebic Keratitis. The genus *Acanthamoeba* consists of several species of free-living amoebae which are receiving increasing attention as causative agents of keratitis and corneal ulceration. Since the first cited case in 1974, there have been a total of twelve published reports of *Acanthamoeba* keratitis in the literature.[2,3,20]

This form of keratitis has generally tended to resist immediate diagnosis. The organisms have been observed in the cornea associated with different pathological states, e.g., as an ulcer, a pseudomembranous conjunctivitis with follicles, a ring-shaped stromal abscess, and a geographic epithelial defect.[2,20] Extreme ocular pain is a prominent symptom in most of the described cases often combined with a severe chemosis which is frequently out of proportion to the degree of keratitis.[3]

The individual species of *Acanthamoeba* can be identified through the use of indirect immunofluorescent techniques. The organism cannot be identified by the morphology of its encysted state alone but requires the reaction with a specific antiserum raised against the appropriate species.

Acanthamoeba keratitis should be suspected in patients with a history of minor corneal trauma. Contact with contaminated water or the presence of an unsterile foreign object in the eye, such as a contact lens, may play a contributing role when the cornea has been rendered more susceptible to infection.[2]

No single treatment for *Acanthamoeba* keratitis exists at the present time. Ketoconazole, an imidazole antifungal agent that has been used widely for mycotic infections, has been suggested as a therapeutic agent by the Centers for Disease Control either alone or in combination with miconazole based on the sensitivity of the organism to these agents established during in vitro testing.[21] Further research will be necessary to determine whether oral administration or topical application of either or both of these drugs will prove effective in eradicating either the trophozoite or encysted stages of the organims causing *Acanthamoeba* keratitis.

Balance of Effort Within Subprogram

There has been a marked shift in emphasis in the thrust of the grants funded in this subprogram between 1981 to 1984. Although 6 grants were aimed at developing therapy to prevent corneal destruction by inflammation in (B2), no grants were funded in this category in either 1983 or 1984 (except for one small grant for pilot projects), despite the recommendation of the Plan for 7 such grants. Most of these grants were reclassified into the establishment of methods for the detection of microorganisms and antigens in corneal tissue (DI) in FY 1982 because of their emphasis on basic mechanisms. This shift represents lessened interest by the eye research community in methods to reduce stromal ulceration, whether it be from viral or other infectious origin. This has resulted in the expansion from 1 grant in FY 1981 to 6 in FY 1984 in the Priority category, a doubling of the 3 recommended by the Plan.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Panel believes that the current Program Base Categories continue to be relevant as does the single Program Development Priority. The latter, however, having exceeded by 3 grants its recommended increase, should now be considered part of the Program Base. New priorities are needed to stress research in onchocerciasis, ocular leprosy, and amoebic keratitis.

Recommended Changes in Program Base and/or Program Development Priorities

As noted above, the Plan's Program Development Priority DI should be moved to the Program Base. Based on the foregoing assessment of recent accomplishments, current activities, and research needs and opportunities in the corneal aspects of onchocerciasis, leprosy, and amoebic infection, the Panel has made the following recommendations concerning additional research in this area over the next two years. These have all been designated as new Program Development Priorities:

1. Establish diagnostic techniques and evaluate the medical therapy for amoebic keratitis.
2. Characterize the infectious agents and immune factors operative in amoebic keratitis; determine factors predictive of the clinical course of this disease.
3. Investigate the specific aspects of the host immunoinflammatory system in onchocerciasis. It may be as important to understand dermal reactivity as a means to prevent microfilariae from reaching the eye as it would be to understand *O. volvulus*-elicited corneal sclerosis and neovascularization.
4. Develop a well-documented epidemiological database that characterizes the amount and extent of ocular morbidity due to *Onchocerca volvulus* in the world's endemic areas.
5. Develop an appropriate animal model for the study of ocular leprosy.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: BACTERIAL, FUNGAL, AMOEBIC, AND PARASITIC KERATITIS (2-E5)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Develop safe methods of delivering antibiotics to ocular tissues. (B1)	2	2	3	1	2	3	2	66.7
2. Develop therapy to prevent corneal destruction by inflammation. (B2)	6	7	0	0	0 [1]	2	1	50.0
TOTAL FOR PROGRAM BASE	8	9	3 [0]	1 [0]	2 [1]	5	3	60.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Establish methods for detection of microorganisms and antigens in corneal tissue. (D1)	1	3	5	6	6	4	4	100.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	3	5 [0]	6 [0]	6 [0]	4	4	100.0
TOTAL FOR SUBPROGRAM	9	12	8 [0]	7 [0]	8 [1]	9	7	77.8
(% OF PROGRAM)	(5.5)	(5.6)	(4.9)	(4.6)	(5.3)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: BACTERIAL, FUNGAL, AMOEBIC, AND PARASITIC KERATITIS (2-E5)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Develop safe methods of delivering antibiotics to ocular tissues. (B1)	SAME	2	2	0	2 [1]	2
2. Develop therapy to prevent corneal destruction by inflammation. (B2)	SAME	0 [1]	2	0	1 [1]	1
3. Establish methods for detection of microorganisms and antigens in corneal tissue. (B3)	MOVED (WAS D1)	6	6	0	4	4
TOTAL FOR PROGRAM BASE		8 [1]	10	0	7 [2]	7 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Establish diagnostic techniques and evaluate the medical therapy for amoebic keratitis. (D1)	NEW	0	1	0	0	0
2. Characterize the infectious agents and immune factors operative in amoebic keratitis; determine factors predictive of the clinical course of this disease. (D2)	NEW	0	3	0	0	0
3. Investigate the specific aspects of the host immuno-inflammatory system in onchocerciasis. (D3)	MOVED (WAS 2-E8 A1)	1 [1]	1	0	1	2
4. Develop a well-documented database that characterizes the amount and extent of ocular morbidity due to Onchoreca volvulus in the world's endemic areas. (D4)	NEW	0	1	0	0	0
5. Develop an appropriate animal model for the study of ocular leprosy. (D5)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		1 [1]	7	0	1 [0]	2 [0]
TOTAL FOR SUBPROGRAM		9 [2]	17	0	8 [2]	9 [0]
(% OF PROGRAM)		(5.8)	(7.8)	(0.0)	(4.8)	(5.2)

Chlamydial Keratoconjunctivitis

Perspective on Recent Research

Chlamydia trachomatis causes both acute and chronic conjunctivitis and is responsible for more corneal blindness in the world than any other infectious agent, affecting some 500 million people and causing blindness in approximately 2 million.[1,2] In its hyperendemic form, seen most frequently in developing nations where good personal hygiene is not always practiced, chronic and recurrent infections lead to scarring of the conjunctiva, lids, and cornea. The agent responsible for this infection is serotyped as A, B, Ba, and C.

In the United States, the *Chlamydia* types found most often in ocular infection are serotypes D-K. Usually the infection is carried from the genital tract to the eyes, where it causes conjunctivitis of a follicular type with concurrent vascular pupillary hypertrophy and more or less subepithelial cellular infiltration. The infection usually does not cause subepithelial scarring of either the conjunctiva or cornea in these cases, presumably because of the lack of chronicity and recurrent infection. However, the diagnosis is frequently not made initially, because of the nonspecific nature of the clinical signs and the lack of a readily available laboratory diagnostic test. Specific therapy in the form of systemic and topical tetracycline is therefore tardily initiated in many cases, leading to prolonged discomfort, temporary visual disability, loss of work, and high medical expense. The nonocular manifestations of chlamydial infection include nongonococcal urethritis, cervicitis, and arthritis. The link between the genital infection and ocular infection has been well established; approximately 60% of women and 40% of men with chlamydial conjunctivitis have concurrent genital infection. This high rate of genital infection has prompted an increased awareness of the need to develop diagnostic tests that are specific, rapid, and low cost, to help eliminate this growing reservoir of infectious agent.[3] In addition, animal models of chlamydial infection continue to be investigated to learn more about infectivity, tissue responses, and therapeutic alternatives.[4] Although much of this work is still directed toward the hyperendemic infections, the growing awareness of the magnitude of the *Chlamydia* problem in developed nations has tended to increase research on both genital and ocular infections.

Recent important developments include the clinical investigation of diagnosis by means of enzyme-linked immunosorbent assay (ELISA) testing for the antigen.[3] This test is done on material from the genital tract and shows in a matter of minutes the presence of the antigen. Although developed to screen for genital infection, there appear to be no limitations in applying this test to material from conjunctival scrapings. If this diagnostic test can be shown to be specific and reliable, it will supplant the slow methods of serum titer determination, the technical problems associated with tissue culture diagnosis, and the low yield of histologic identification of the infectious agent.

Progress in Areas Discussed in the 1983-87 Plan

One of the objectives in the Plan is that mentioned above: to develop rapid, practical, and reliable methods for diagnosing chlamydial keratoconjunctivitis. Several centers in the United States are now evaluating the specificity and reliability of the ELISA test for ocular chlamydia. It is likely that commercial support will take over the large-scale testing necessary to develop a widely available test. Initial results indicate that this test may offer significant advantages over currently available methods.

Unfortunately, little progress has been made on two other specific objectives. These are to define the role of local and systemic immunity in primary infection and re-infection by *C. trachomatis* and to define the optimal method of preventing neonatal ocular and nonocular infections. In part, the failure to achieve these goals is related to the difficulty in establishing appropriate animal models for the disease. However, both serum antibodies and cell-mediated immune responses have been studied in the guinea pig, but the agent (*C. psittaci*) is found in a variety of animals and may not mimic very closely the course of human disease.[5,6]

Prevention of neonatal chlamydial infection continues to be difficult because of both a lack of prepartum diagnosis in the mother and a safe prophylaxis for the newborn. These remain high priority goals for infectious disease researchers.

New and Developing Areas of Research

Monoclonal antibodies to the chlamydial agent are likely to prove of great value in improving diagnosis of this disease. Fluorescent monoclonal antibodies would permit positive identification of the agent in both scrapings and tissue sections of infected tissue.

The development of a specific vaccine for *Chlamydia* seems more likely now that methods of recombinant DNA research make purification of the chlamydial polypeptides possible. The understanding of the mechanisms of resistance and immunity to *C. trachomatis* must be sought in animal models that closely mimic the human disease.

Balance of Effort in Subprograms

In FY 1984, the National Eye Institute funded 6 grants for research on chlamydial keratoconjunctivitis. Three of these grants were related to defining the role of immunity in chlamydial keratoconjunctivitis, two were for the prevention of neonatal infection, and one was to develop rapid methods for diagnosis of ocular chlamydial infections. There has been no growth in the number of grants funded for chlamydia research, despite its growing importance in the etiology of both ocular and nonocular infection.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

In reviewing the Plan's categorization of research in this area, the Panel judges them still to be relevant and important; however, the development of new diagnostic methods is now being carried out by the commercial sector.

Recommended Changes in Program Base and/or Program Development Priorities

The potential commercial development of a rapid method for the detection of ocular chlamydial infection led the Panel to recommend that this recommendation (DI) be moved from the category of Program Development Priority to the Program Base. The Panel continues to recommend the addition of one grant to this category, as well as the addition of one grant to the category of defining the role of immunity (BI). A reduction by one grant in category B2 should maintain funding in this category at an adequate level.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: CHLAMYDIAL KERATOCONJUNCTIVITIS (2-E6)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Define role of immunity in chlamydial keratoconjunctivitis. (B1)	5	5	6	4	3	4	1	25.0
2. Prevent neonatal chlamydial infections. (B2)	1	1	0	2	2	5	2	40.0
TOTAL FOR PROGRAM BASE	6	6	6 [0]	6 [0]	5 [0]	9	3	33.3
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop rapid methods for diagnosis of ocular chlamydial infections. (D1)	1	2	1	1	1	1	1	100.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	2	1 [0]	1 [0]	1 [0]	1	1	100.0
TOTAL FOR SUBPROGRAM	7	8	7 [0]	7 [0]	6 [0]	10	4	40.0
(% OF PROGRAM)	(4.3)	(3.7)	(4.3)	(4.6)	(3.9)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: CHLAMYDIAL KERATOCONJUNCTIVITIS (2-E6)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Define role of immunity in chlamydial keratoconjunctivitis. (B1)	SAME	3	4	0	1	1
2. Prevent neonatal chlamydial infections. (B2)	SAME	2	1	1	3	3
3. Develop rapid methods for diagnosis of ocular chlamydial infections. (B3)	MOVED (WAS D1)	1	2	0	1	1
TOTAL FOR PROGRAM BASE		6 [0]	7	1	5 [0]	5 [0]
TOTAL FOR SUBPROGRAM		6 [0]	7	1	5 [0]	5 [0]
(% OF PROGRAM)		(3.9)	(3.2)	(5.0)	(3.0)	(2.9)

Chronic Blepharitis

Perspective on Recent Research

There have been no significant changes in this field of research since the Plan was published.

Progress in Areas Discussed in the 1983-1987 Plan

The composition of normal tear lipids and meibomian gland secretions, which was the subject of Program Development Priority Dl, has largely been determined. Work is in progress on analyzing the composition of these substances in tears and meibomian gland secretions from patients with chronic blepharitis. The pathogenesis of these entities is not yet known.

New and Developing Areas of Research

There are no new research techniques or new information from other research fields that might be applied to research on chronic blepharitis with the assurance that important new information will be obtained.

Balance of Effort Within Subprogram

Funding has increased slightly since FY 1981 along the lines recommended in the Plan in Priority Dl. A single grant was recommended for the study of the pathogenesis of chronic blepharitis and associated keratoconjunctivitis, D2, but this Program Development Priority has not yet been achieved.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

There is currently enough information on the composition of normal tear lipids and meibomian secretions and their comparisons with tears and secretions from chronic blepharitis patients. Work still needs to be done on determining the pathogenesis of chronic blepharitis and associated keratoconjunctivitis and on developing therapeutic modalities. This area of research appears to be ready for new approaches based upon advances in dermatological research.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends moving Priority Dl to the Program Base and retaining D2 and the single Program Development Priority.

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: CHRONIC BLEPHARITIS (2-E7)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1. Establish composition of normal tear lipids and meibomian secretions and compare to blepharitis patients. (D1)	2	3	2	3	3	1	1	100.0
2. Determine pathogenesis of chronic blepharitis and associated keratoconjunctivitis and develop therapeutic modalities. (D2)	0	1	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	2	4	2 [0]	3 [0]	3 [0]	1	1	100.0
TOTAL FOR SUBPROGRAM	2	4	2 [0]	3 [0]	3 [0]	1	1	100.0
(% OF PROGRAM)	(1.2)	(1.9)	(1.2)	(2.0)	(2.0)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: CHRONIC BLEPHARITIS (2-E7)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Establish composition of normal tear lipids and meibomian secretions and compare to blepharitis patients. (B1)	MOVED (WAS D1)	3	3	0	3	2
TOTAL FOR PROGRAM BASE		3 [0]	3	0	3 [0]	2 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Determine pathogenesis of chronic blepharitis and associated keratoconjunctivitis and develop therapeutic modalities. (D1)	SAME (WAS D2)	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	1	0	0 [0]	0 [0]
TOTAL FOR SUBPROGRAM		3 [0]	4	0	3 [0]	2 [0]
(% OF PROGRAM)		(1.9)	(1.8)	(0.0)	(1.8)	(1.2)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

EXTERNAL OCULAR INFECTIONS AND INFLAMMATORY DISEASES: OTHER INFECTIONS (2-E8)*

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Other. (A1)	2	2	2 [1]	1	1 [1]	8	2	25.0
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	2	2	2 [1]	1 [0]	1 [1]	8	2	25.0
TOTAL FOR SUBPROGRAM	2	2	2 [1]	1 [0]	1 [1]	8	2	25.0
(% OF PROGRAM)	(1.2)	(0.9)	(1.2)	(0.7)	(0.7)			

*This subprogram transferred to Subprogram 2-E5 in Revised Subprogram Resource Table.

Ocular Surface Problems

2

Perspective on Recent Research

Ocular surface disorders continue to be of great importance because of their relative frequency and their severity. These disorders involve the tear film, the conjunctiva, and the cornea and cause redness, discharge, photophobia, pain, and reduced vision. In some cases the abnormalities lead to ulceration and scarring of both the cornea and conjunctiva, resulting in permanent disability.

A. Tear Film and Its Abnormalities

Since the publication of the Plan, considerable attention has been focused on the tear film and its role in maintaining the health of the ocular surface cells. A recent Tear Film Symposium at Texas Tech University in Lubbock, sponsored by the National Eye Institute, brought together researchers from the United States and many foreign countries to discuss the current status of tear film research and therapy.[1] The program was organized into sections on diagnosis, treatment, ocular surface disorders, pathophysiology, tear flow and tear film formation, tear film and contact lens wear, meibomian lipids, lacrimal glands, and tear composition. The outcome of these deliberations was to renew scientific interest in the tear layer, and to focus current research techniques on improving understanding of tear film composition and function.

B. Ocular Surface Disorders

The biology of the ocular surface epithelial cells is better understood than it was when the Plan was written. For example, healing of conjunctival wounds has now been shown to involve sliding of cells to cover the defect, with a concurrent loss of goblet cells in the sliding epithelium.[2] The inverse relationship between surface cell mitosis and the state of differentiation of the cells suggests that disease characterized by a high rate of epithelial cell mitosis might be treated by direct modulation of surface cell mitosis through local or systemic medication.[3]

Clinical advances in the management of ocular surface diseases include the increased use of immunosuppression for control of surface disease with presumed autoimmune etiology,[4] and the use of vitamin A supplementation to alter the differentiation of the ocular surface cells.[5]

C. Drug Delivery and Toxicity

Drug penetration and toxic effects on the ocular surface have been relatively inactive areas of research for the past three years. However, the recognition of an increasing number of cases of surface cell toxicity from the preservatives used to maintain sterility in eye drops makes the study of drug-cell interactions of even greater importance.[6] A recent development in epithelial cell culture permits growth of large quantities of surface cells, which should facilitate toxicity studies in the laboratory without the need for large numbers of animals.[7]

Progress in Areas Discussed in the 1983-1987 Plan

A. Tear Film and Its Abnormalities

A noteworthy conclusion of the Tear Film Symposium was the recognition of the extreme complexity of the tear film. The participants reached a consensus on the need for better standardized tear collection techniques. Scientific data has provided evidence that the permeability of the ocular surface will greatly affect tear film composition as a result of leakage of serum proteins.[8,9] Lactoferrin was recognized as a tear protein with antibacterial action as important, or perhaps even more important, than that function ascribed to lysozyme.[10] Tear film breakup time was noted to be quite variable in normal as well as in diseased individuals, with the variance of results from successive tests in one individual many times greater than among individuals.

The Schirmer test was considered to be significantly affected by evaporation unless care was taken to prevent this phenomenon by use of a smaller length of filter paper for wetting or a plastic sleeve.[11] Impression cytology has become better standardized as a technique for the study of ocular surface disease states and has extended solely from the counting of goblet cells to the characterization of ocular surface cytology.[12] Ocular surface cells were noted to lose their microplicae in the presence of a hypertonic tear film.[13] Tear evaporation can be measured by a new technique which has shown that dry eyes have an increased rate of evaporation.[14]

B. Ocular Surface Disorders

Tissue culture of ocular surface epithelial cells continues to yield important information regarding both the normal and pathologic metabolic processes responsible for cell division, adhesion, and longevity. The development of enriched culture media has facilitated studies of cell surface receptors and the effect of humoral mediators on cell viability.[7,15]

A provocative observation is that the application of topical retinoids may in some way reverse the symptoms found in dry eyes.[5] This observation needs confirmation, with delineation of the types of dry eye conditions which can be improved with the use of topical vitamin A compounds. Of great importance is the need to clarify the effects of these compounds on the eye. Do they relieve symptoms by reducing squamous metaplasia and enhancing wetting of the surface, or do they cause an increase in aqueous tear production?

The use of mitogens to encourage reepithelialization of the cornea has been disappointing so far. A clinical study that employed epidermal growth factor was found not to speed epithelial healing in patients.[16] The use of fibronectin to enhance epithelial healing has been investigated.[17] Favorable results obtained in cell culture with this protein have been reinforced by a study in patients that also ascribed better healing to the use of fibronectin drops.[18] Such results require confirmation in larger groups of patients to establish the clinical efficacy of this therapy.

The use of immunosupressive agents to ameliorate the adverse evolution of the presumed autoimmune diseases (ocular cicatricial pemphigoid (OCP), rheumatoid arthritis, and Stevens-Johnson syndrome) continues to gain acceptance by both ophthalmologists and internists alike.[4] The observation that OCP is associated with hyperproliferation of the conjunctival epithelium[3] has stimulated investigation of other ocular surface diseases that may share this pathophysiologic mechanism. Another feature of these diseases is squamous metaplasia, which has been elucidated by Tseng and co-workers.[19] Early observations suggest that topical vitamin A therapy may alter this abnormal surface differentiation and prevent both surface scarring and its attendant dry eye. More studies are required to delineate the cases in which control of surface differentiation is beneficial.

The apparent increased vulnerability of the ocular surface in vitamin A deficiency is being investigated in laboratory studies.[20] Vitamin A deficient rabbits are being challenged with a variety of surface lesions in an attempt to mimic the clinical situation found in children who are vitamin A deficient. Clinical studies of the abnormalities of the ocular surface in vitamin A deficient children in developing nations are underway to elucidate the mechanism responsible for the high incidence of blindness associated with measles and other infections.

C. Drug Delivery and Toxicity

The high incidence of corneal epithelial abnormalities associated with the frequent use of drugs containing antibacterial preservatives has been documented by clinical studies.[6] Only recently has a tissue culture technique been devised that promises to facilitate wide-scale laboratory testing for potential drug toxicity without the need for large numbers of live animals.[21] This approach to reduce the need for the Draize test represents a major step forward in evaluating ocular drug toxicity.

New and Developing Areas of Research

A. Tear Film and Its Abnormalities

The evaluation of and effective therapy for patients with tear dysfunction continues to pose considerable problems because of inadequate methods of tear collection and analysis of tear components. The analysis of the tear film interface at the ocular surface and its behavior in the presence of tear film deficiencies as measured by determinations of osmolarity, tear proteins, and ocular surface cytology is of particular significance. The production of specific antiserum to tear constituents may now be facilitated by the use of monoclonal antibody, which should permit more precise tear analysis and give new information about the cellular origin of various tear components. Suitable organ and cell culture systems could yield important new information about the differentiation of lacrimal and meibomian glands, thus explaining changes observed in those glands with aging.

Tear composition in normals, lacrimal function and control mechanisms, and lid function in the resurfacing of the tear film require further analysis to establish significant variations in disease states. In addition, the relative role of lacrimal gland dysfunction and mechanical blockage of the ducts connecting the gland to the upper fornix must be determined. The potential worth of lacrimal secretagogues, although being actively studied in Europe, has received almost no attention from researchers in the United States. Bromhexine, eledoisin, and physalaemin are mentioned in the literature, but work on such kinins should be pursued. This research could also be extended to include the effect of a variety of commonly prescribed systemic medications on lacrimal flow.

B. Ocular Surface Disorders

Since the publication of the Plan, exciting developments in immunology, molecular biology, and neurobiology have enhanced the possibilities for significant progress in the study of the ocular surface and its disorders. For example, the production of monoclonal antibodies specific for a wide range of tissue antigens has permitted highly sophisticated studies of diseases such as ocular cicatricial pemphigoid (OCP), which permit greater specificity in diagnosis and which have established these diseases as autoimmune in etiology.

The use of monoclonal antibodies has also become a powerful tool for the study of cellular differentiation, thereby allowing study of the role of the extracellular environment on the production and secretion of cellular products. Although monoclonal antibody techniques have been adequately developed to investigate cell differentiation on experimental tissues, their use on material derived from patients is still incomplete. The state of differentiation of the ocular surface (goblet cell-containing, metaplastic, or keratinized) can probably be detected much earlier in the evolution of surface diseases with the use of monoclonal antibodies to the intracellular keratins and cell surface proteins.

The use of genetic "probes" to determine the expression of DNA in cells has facilitated fundamental studies of control of cellular differentiation. Such molecular biology can now be applied to understanding the changes in differentiation that occur in epithelial cells in the presence of excess quantities of vitamin A, for example. If tissue culture methods can be developed that permit retention of the abnormal growth and differentiation of ocular surface cells from patients, the abnormal as well as normal control processes can be understood and possibly modified.

Persistent corneal epithelial defects continue to be the most frequent manifestation of ocular surface disease. While hypotheses have been formulated to take into account all of the factors that might go contribute to the loss of epithelial tissue,[22] the various clinical characteristics of these defects is still poorly understood. In what cases are the tissue losses secondary to a lack of mitosis, a lack of cell sheet sliding, or a lack of cellular basement membrane stromal adhesion? The answer to these questions will come from more systemic studies of the clinical cause of these defects, correlated with biochemical and immunologic analyses of tissue specimens from affected patients.

Recent work in the use of cryolathed corneal stromal lenticules to change the refractive strength of the cornea suggests that there may be important interactions between the subepithelial keratocytes of the stroma and the overlying epithelium. A similar epithelial cell keratocyte interaction may be present in the cicatricial diseases such as OCP. Tissue culture techniques now permit sophisticated studies of the effect of keratocyte-secreted matrix materials on epithelial cells, as well as the effect of epithelial products on keratocyte and vascular endothelial metabolic control. Such studies are particularly relevant now and promise to suggest mechanisms for control of both subepithelial scarring and vascularization.

C. Drug Delivery and Toxicity

As noted in the preceding section, tissue culture techniques using ocular surface cells have been recently developed to study the adverse effects of topically applied drugs and their preservatives. Not only may may this development permit a reduction in the number of animals needed for toxicity studies, it may also speed the demonstration of safety and efficacy required to win FDA marketing approval for ocular medications. This tissue culture system should be expanded to lines of human ocular surface cells, and should include tests for mitotic rates and adhesion as well as cell sheet sliding.

Liposomes have been thought to be a useful vehicle to augment transport of various substances into the corneal stroma. The use of these substances to enhance penetration of antibiotics and antivirals and to prolong contact times of medication with the ocular surface is an exciting possibility that should be explored in animal models.

Balance of Effort Within Subprogram

A. Tear Film and Its Abnormalities

There were two significant shifts in the relative emphasis within the Program Base and the Program Development Priorities in this subprogram area since 1981. First, there was more growth than anticipated in category B1, to investigate the normal composition, function, and control mechanisms of the preocular tear film, which doubled from two to four projects by FY 1984. One additional small grant for pilot projects was also funded in this area in FY 1984. (Subsequent to this report, one additional grant was reclassified from category B3 to B1 for a total of five projects for FY 1984.) There was a sharp reduction in the number of grants to evaluate and treat dry eye patients more effectively (B3), declining from six grants in 1981 to one (after reclassifying one grant to B1) in 1984.

The two grants funded in Program Development Priority D1 in FY 1984, to determine the relationship between the preocular tear film and the ocular surface, fall one short of the three recommended by the Plan.

B. Ocular Surface Disorders

There has been some reduction in the number of grants related to epithelial healing (B1) since FY 1981. At that time 12 grants were supported; the Plan called for a reduction to 11 by FY 1983. In FY 1984 only eight were funded; however, one of these was subsequently reclassified to D4 in Chapter Three, The Correction of Refractive Error. This reduction is due in part to the lack of innovative approaches in this area, as reflected in grant applications that have been less competitive.

The search for conjunctival antigens responsible for the immune phenomena in ocular surface disorders (B2) has shown modest growth from one to three grants, exceeding the Plan's recommendations in this category.

In the Program Development Priorities, growth did occur along the lines envisioned by the Plan in most categories at some time during the period FY 1982 to FY 1984, although there was a falling off in the number of additional grants awarded in D4 and D5 by FY 1984. In category D2, to analyze epithelial defects in relation to basement membrane changes and stromal ulceration, the Plan's recommendation to increase the 6 grants funded in FY 1981 to 8 by FY 1984 was not only not realized, the number of grants was reduced to only 3 funded grants in FY 1984.

C. Drug Delivery and Toxicity

The effort devoted to pursuing subjects in this area in FY 1984 coincides exactly with the recommendation of the Plan, which called for 2 grants directed toward understanding the immunological reaction to conjunctivally applied antigens.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

A. Tear Film and Its Abnormalities

The emphasis on classic composition and function studies should be augmented by new studies on the cellular origin of the tear components. In particular, the physiology of the lacrimal gland warrants further clarification. In addition, the relative role of gland dysfunction versus gland excretory obstruction at the level of the ducts connecting the gland to the upper fornix should be determined. Tissue culture studies of lacrimal gland may permit evaluation of secretagogues or the inhibitor effects exerted by inflammatory cells. The use of monoclonal antibodies should permit in vivo evaluation of mucous production and spreading.

B. Ocular Surface Disorders

The Program Base and Program Development Priorities continue to be relevant. Emphasis should also be given to the evaluation of the interactions of the ocular surface epithelium and subjacent keratocytes in conjunctival scar formation.

C. Drug Delivery and Toxicity

As initially categorized, this subprogram had no Program Base. It is appropriate that the work now funded on the immunological reactions to conjunctivally applied antigens serve as the Base for this subprogram area.

Recommended Changes in Program Base and/or Program Development Priorities

A. Tear Film and its Abnormalities

The Panel recommends that the Program Base in this subprogram remain the same with a slight rewording of category B2 to focus attention on the role of cellular origins in addition to the lids in ocular resurfacing by the tear film.

The Panel recommends a considerable increase in the number of Program Development Priorities. These are: the preparation and use of monoclonal antibodies to various tear components, goblet cells, and cells of lacrimal and meibomian glands to define the cellular origin of various tear components; the study of lacrimal and meibomian gland differentiation in organ and cell culture; and the determination of the relative roles of lacrimal gland dysfunction and duct obstruction in the production of dry eye in ocular surface disease.

B. Ocular Surface Disorders

All of the Plan's Program Base and Program Development Priorities in this area should remain the same. One additional Priority is recommended: Evaluate the interaction of the ocular surface epithelium and subjacent keratocytes and matrix in conjunctival scar formation.

C. Drug Delivery and Toxicity

The Panel recommends a new Program Development Priority: the development of new and innovative methods of drug delivery in ocular surface disorders.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

OCULAR SURFACE PROBLEMS: TEAR FILM AND ITS ABNORMALITIES (2-F2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Applications FY 1983-84 Funded	Applications FY 1983-84 Percent
PROGRAM BASE								
1. Investigate normal composition, function, and control mechanisms of preocular tear film. (B1)	2	2	1	2	4 [1]	7	4	57.1
2. Determine role of lids in ocular resurfacing by tear film. (B2)	1	1	2	1	1	0	0	
3. Evaluate and treat dry eye patients more effectively. (B3)	6	5	5	4	2	4	2	50.0
TOTAL FOR PROGRAM BASE	9	8	8 [0]	7 [0]	7 [1]	11	6	54.5
PROGRAM DEVELOPMENT PRIORITIES								
1. Determine interrelationship between preocular tear film and ocular surface. (D1)	1	3	2	2	2	2	1	50.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	3	2 [0]	2 [0]	2 [0]	2	1	50.0
TOTAL FOR SUBPROGRAM	10	11	10 [0]	9 [0]	9 [1]	13	7	53.8
(% OF PROGRAM)	(6.2)	(5.1)	(6.1)	(5.9)	(5.9)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

OCULAR SURFACE PROBLEMS: TEAR FILM AND ITS ABNORMALITIES (2-F2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Investigate normal composition, function, and control mechanisms of preocular tear film. (B1)	SAME	3 [1]	5	0	2 [1]	2
2. Determine role of lids and cellular origins in ocular resurfacing by tear film. (B2)	EXPANDED	1	2	0	0	0
3. Evaluate and treat dry eye patients more effectively. (B3)	SAME	1	3	0	1	1 [1]
TOTAL FOR PROGRAM BASE		5 [1]	10	0	3 [1]	3 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Determine interrelationship between preocular tear film and ocular surface. (D1)	SAME	2	3	0	3	4
2. Prepare monoclonal antibodies to various tear components, conjunctival goblet cells, and cells of lacrimal and meibomian glands, and use these antibodies to define the cellular origin of various tear components. (D2)	NEW	0	2	0	0	0
3. Develop suitable organ and cell culture systems for studying in vitro lacrimal and meibomian gland differentation. (D3)	NEW	2	1	0	2 [1]	2
4. Determine the relative roles of lacrimal gland dysfunction and duct obstruction in the production of dry eye in ocular surface disease. (D4)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		4 [0]	7	0	5 [1]	6 [0]
ADDITIONAL RESEARCH CATEGORIES						
1. Other. (A1)		0	0	0	0	1
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES		0 [0]	0	0	0 [0]	1 [0]
TOTAL FOR SUBPROGRAM		9 [1]	17	0	8 [2]	10 [1]
(% OF PROGRAM)		(5.8)	(7.8)	(0.0)	(4.8)	(5.8)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

OCULAR SURFACE PROBLEMS: OCULAR SURFACE DISORDERS (2-F3)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Study epithelial healing. (B1)	12	11	10 [1]	8	8	11	4	36.4
2. Search for conjunctival antigens responsible for immune phenomena in ocular surface diseases. (B2)	1	1	2	2	3	2	1	50.0
TOTAL FOR PROGRAM BASE	13	12	12 [1]	10 [0]	11 [0]	13	5	38.5
PROGRAM DEVELOPMENT PRIORITIES								
1. Investigate epithelial defect formation, occurrence, and persistence and relationship with neural supply. (D1)	2	3	2	3 [1]	3	6	3	50.0
2. Analyze epithelial defects in relation to basement membrane changes and stromal ulceration. (D2)	6	8	5	3 [1]	3	8	4	50.0
3. Study ocular surface epithelium as maintained by conjunctiva. (D3)	1	2	1 [1]	2	2	4	2	50.0
4. Evaluate normal immunologic mechanisms of ocular surface. (D4)	6	7	7	6 [1]	5	8	6	75.0
5. Evaluate stimuli for corneal vascularization and conjunctiva ingrowth onto ocular surface. (D5)	2	3	3	3	2 [1]	4	1	25.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	17	23	18 [1]	17 [3]	15 [1]	30	16	53.3
TOTAL FOR SUBPROGRAM	30	35	30 [2]	27 [3]	26 [1]	43	21	48.8
(% OF PROGRAM)	(18.5)	(16.3)	(18.4)	(17.8)	(17.1)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

OCULAR SURFACE PROBLEMS: OCULAR SURFACE DISORDERS (2-F3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Study epithelial healing. (B1)	SAME	8	9	0	10 [1]	9 [1]
2. Search for conjunctival antigens responsible for immune phenomena in ocular surface diseases. (B2)	SAME	3	3	0	2	2
TOTAL FOR PROGRAM BASE		11 [0]	12	0	12 [1]	11 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Investigate epithelial defect formation, occurrence, and persistence and relationship with neural supply. (D1)	SAME	4	4	0	3	2
2. Analyze epithelial defects in relation to basement membrane changes and stromal ulceration. (D2)	SAME	3	4	0	3	3 [1]
3. Study ocular surface epithelium as maintained by conjunctiva. (D3)	SAME	2	2	0	2	1
4. Evaluate normal immunologic mechanisms of ocular surface. (D4)	SAME	5	7	0	7	7 [1]
5. Evaluate stimuli for corneal vascularization and conjunctival growth onto ocular surface. (D5)	SAME	2 [1]	3	0	2	3
6. Evaluate interaction of ocular surface epithelium and subjacent fibrocytes and matrix in conjunctival scar formation. (D6)	NEW	0	2	0	1	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		16 [1]	22	0	18 [0]	17 [2]
TOTAL FOR SUBPROGRAM		27 [1]	34	0	30 [1]	28 [3]
(% OF PROGRAM)		(17.5)	(15.7)	(0.0)	(18.0)	(16.3)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

OCULAR SURFACE PROBLEMS: DRUG DELIVERY AND TOXICITY (2-F4)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects EY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM DEVELOPMENT PRIORITIES								
1. Understand immunological reactions to conjunctivally applied antigens. (D1)	1	2	1	1	2	3	2	66.7
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	2	1 [0]	1 [0]	2 [0]	3	2	66.7
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Other. (A1)	0	0	0 [1]	0	0 [2]	2	2	100.0
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	0	0	0 [1]	0 [0]	0 [2]	2	2	100.0
TOTAL FOR SUBPROGRAM	1	2	1 [1]	1 [0]	2 [2]	5	4	80.0
(% OF PROGRAM)	(0.6)	(0.9)	(0.6)	(0.7)	(1.3)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

OCULAR SURFACE PROBLEMS: DRUG DELIVERY AND TOXICITY (2-F4)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Understand immunological reactions to conjunctivally applied antigens. (B1)	MOVED (WAS D1)	2	2	0	3	3
TOTAL FOR PROGRAM BASE		2 [0]	2	0	3 [0]	3 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop new and innovative methods of drug delivery in ocular surface disorders. (D1)	NEW	0 [2]	2	0	0	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [2]	2	0	0 [0]	1 [0]
ADDITIONAL RESEARCH CATEGORIES						
1. Other. (A1)		0	0	0	0 [1]	1
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES		0 [0]	0	0	0 [1]	1 [0]
TOTAL FOR SUBPROGRAM		2 [2]	4	0	3 [1]	5 [0]
(% OF PROGRAM)		(1.3)	(1.8)	(0.0)	(1.8)	(2.9)

Correction of Refractive Errors

3

Perspective on Recent Research

Considerable progress has been made in the contact lens field in the years since publication of the Plan, including the development of new lenses that patients may wear for extended periods of time without removal. Several types of such lenses are now on the market reflecting the great demand for extended-wear flexible lenses by myopic, astigmatic, presbyotic and aphakic patients. Also, the FDA has approved the marketing of daily-wear gas-permeable rigid contact lenses.

Much research has been directed toward the effect of contact lens wear on the cornea and conjunctiva. Infectious and noninfectious inflammatory complications have been investigated. The concomitant use of topical medications and contact lenses has also been studied.

Recent studies of orthokeratology, a contact lens technique designed to gradually flatten corneal curvature and reduce myopia, have shown that functional refractive error fluctuated during the treatment follow-up period and that the induced changes were not permanent. The lack of persistent change indicates that the cornea is either highly elastic or has some other memory mechanism. Although orthokeratology produces modest reductions in myopia, the effect does not persist without continued lens wear.

Intraocular lenses continue to be used increasingly for the visual correction of aphakia following cataract removal. Patients who suffer visual loss from a combination of cataract and corneal opacification have benefited increasingly over recent years by sight restoration involving a combination of cataract extraction with intraocular lens implantation and corneal transplantation.

The field of keratorefractive surgery has been very active over the past several years. Advances have been made in electrosurgical keratoplasty which is used to treat patients with mild to moderate keratoconus in an effort to avoid corneal transplantation. This stromal collagen alteration technique may be useful in patients with abnormal corneal shape as an alternative to transplant surgery.

A detailed investigation of radial keratotomy has been initiated in the National Eye Institute supported-Prospective Evaluation of Radial Keratotomy (PERK) study. Early results show that the procedure is capable of reducing low and moderate amounts of myopia; however, accurate predictability of results remains a problem.[23]

Early results of epikeratophakia—a procedure in which a donor cornea that has been frozen and ground on a lathe to achieve the proper refractive correction is attached to the front surface of the recipient's cornea—have shown that this surgical procedure may be useful in the management of aphakia and higher degrees of myopia that cannot be corrected by conventional means.

In keratomileusis, a procedure similar to epikeratophakia, a portion of the patient's cornea is removed, frozen, ground on a lathe to the proper corrective refraction, and then reattached to the cornea. A recent prospective study of myopic keratomileusis has demonstrated an average reduction of myopia by 11.5 diopters, offering another alternative method for surgical correction of higher degrees of myopia.[38]

The use of intrastromal hydrogel lenses for the surgical correction of aphakia is an exciting new area of research that has not yet been evaluated clinically. However, it has shown promise in animal models over the past several years.

Progress in Areas Discussed in the 1983-1987 Plan

In addition to research which has resulted in the development and FDA approval of new extended wear and gas-permeable contact lenses[1], much effort has been dedicated to the study of effects of contact lenses on the cornea and surrounding tissues. It has been found that contact lens wear can suppress epithelial cell mitosis and increase aqueous humor lactate concentration, the degree of changes becoming greater as the permeability of the lens to oxygen decreased and the period of wear became longer.[2] Studies have demonstrated a relationship between contact lens-induced corneal swelling and oxygen deprivation.[3,4]

In extended-wear, the level of daytime corneal edema was determined primarily by the overnight swelling.[5] Thin gas-permeable lenses produced less corneal swelling than thicker polymethylmetnacrylate (PMMA) lenses.[6] Transient endothelial changes were observed by specular and electron microscopy following the use of thick, low water content, soft contact lenses.[7]

Less contact lens-associated corneal swelling was found in aphakic eyes compared to phakic eyes, as a result of either a reduction in the overall metabolic activity of the epithelium or an increased efflux of lactic acid from the cornea due to increased endothelial permeability to lactate in the aphakic eye.[8] Extended-wear contact lenses after penetrating keratoplasty in aphakic eyes were found to induce graft vascularization, which may predispose such eyes to special risks such as graft rejection.[9,10]

Studies have been conducted on the effect of topical administration of drugs over contact lenses. The combined use of contact lenses and timolol has been observed to produce marked alterations in both corneal epithelium and endothelium.[11] The permeability of gentamicin topically administered to hydrogel bandage contact lenses was found to be negligible; the important drug distribution pathway was around the edge of the lens.[12]

Bacterial corneal ulcers have been reported with extended-wear soft contact lenses in myopic and aphakic eyes.[13-15] Also, noninfectious corneal and conjunctival inflammatory changes associated with contact lens wearing have been investigated, including giant papillary conjunctivitis[16], and superior limbic keratoconjunctivitis.[17] The etiology of the latter complication may be related to an allergic response to contact lens solution preservatives.

A National Eye Institute-supported study of orthokeratology—a single center, randomized controlled clinical trial—found that with this procedure myopia could be reduced by about 1 diopter. However, the changes were not permanent. The lack of persistent change indicates that the cornea is either highly elastic or has some other memory mechanism.[18] Although orthokeratology produces modest reductions in myopia, the effect does not persist without continued contact lens wear.

Intraocular lenses are used increasingly for the visual correction of aphakia following cataract removal. They provide nearly optimal correction, and patients who receive lens implants achieve good vision immediately after surgery and maintain it 24 hours a day. This form of correction is especially important to patients who would have difficulty inserting and removing contact lenses.

Recently, lens implants have been used successfully with corneal transplants so that patients who suffer visual loss from a combination of cataract and corneal opacification may have sight restored by cataract extraction combined with intraocular lens implantation and corneal transplantation.[19]

Attempts to shrink the collagen of the cornea to flatten the corneal curvature have been reported (thermokeratoplasty, Los Alamos keratoplasty). However, thermokeratoplasty is not used on a routine basis clinically because it tends to damage the endothelial and epithelial basement membranes and usually produces temporary results. Recently, use of a microprobe for applying heat to create collagen denaturation (Los Alamos keratoplasty technique) has permitted focal collagen shrinking without spreading thermal damage to the endothelium or epithelium.[20] The Los Alamos electrosurgical keratoplasty procedure has been used to treat patients with mild to moderate keratoconus in an effort to avoid corneal transplantation.[21] Patients returned to contact lens wear four weeks postoperatively. This stromal collagen alteration technique may be applicable in patients with keratoconus, without apical scarring, as an alternative to transplant surgery.

Another technique to reduce corneal curvature in nearsighted patients, radial keratotomy, was introduced in the USSR in 1974[22] and in the United States in late 1979. Within six years, more than 100,000 patients underwent the procedure in this country. The National Eye Institute has supported a clinical trial of radial keratotomy—The Prospective Evaluation of Radial Keratotomy (PERK) study—a multicenter, self-controlled study of a standardized technique of radial keratotomy in patients with a preoperative refraction between -2.00 and -8.00 diopters.[23] At one year after surgery, myopia was reduced in all eyes: 60% were within ± 1.00 diopter of emmetropia, 30% were undercorrected and 10% were overcorrected by more than 1.00 diopter. Uncorrected visual acuity was 20/40 or better in 78% of eyes. The operation was most effective in eyes with a refraction between -2.00 and -4.25 diopters. Between six months and one year after surgery, the refraction changed by $\geq$ 0.50 diopters in 19% of eyes. The results three years after radial keratotomy indicate that although few severe complications have been noted, predictability of the results remains a problem—57 percent remain corrected within 1 diopter, 27 percent are undercorrected, and 16 percent are overcorrected.[24]

Other clinical trials have also demonstrated that radial incisions do reduce myopia;[25,26] however, accurate predictability remains a problem. Many patients still require glasses or contact lenses for best corrected vision after the radial keratotomy procedure[27], and a few may not be able to regain their preoperative vision even with correction. Psychosocial studies found that impatience with contact lenses was the major motivation for wanting radial keratotomy.[28] Postoperatively, corneal epithelial abnormalities have been observed in patients, including iron lines[29] and map-fingerprint-dot changes.[30] In animal studies, endothelial cell loss was detected[31,32] and susceptibility to traumatic rupture was increased following radial keratotomy.[33]

Epikeratophakia has been performed in children for the correction of aphakia after the removal of unilateral congenital or traumatic cataracts. The average increase in corneal refractive power ranged from 12.5 to nearly 15 diopters.[34] By attaching the correction permanently on the eye, epikeratophakia may facilitate the vigorous occlusion therapy to reverse amblyopia required after cataract extraction in these children.[35] The epikeratophakia procedure has also been performed in adult aphakic patients who achieved 87% of predicted dioptoric correction in a recent series.[36] Visual acuities improved with time and were best with hard contact lenses as a result of irregular refraction at the graft surface. Epikeratophakia has also been performed for the correction of keratoconus[37] and myopia[38], with up to 37.5 diopters of myopic correction obtained: a mean increase of one-half diopter cylinder was found.

A recent prospective evaluation of myopic keratomileusis revealed an average reduction of myopia by 11.5 diopters: there was no change in the refractive cylinder.[39] The final refraction took up to six months to stabilize. The technique is difficult but may be useful in the visual rehabilitation of the high myope. Myopic keratomileusis has been studied in a baboon model using the same instruments and techniques that are presently employed clinically.[40] No technical problems were encountered at surgery or during the six-month postoperative follow-up period. A wide range of central corneal thickness of the excised corneas accounted for the undercorrections achieved. The baboon model is considered to be excellent for the evaluation of myopic keratomileusis.

Another type of lamellar surgical refractive procedure employs the use of intrastromal hydrogel lenses.[41] Convex-shaped, hydrophilic lenticles of various water content have been implanted into microkeratome-dissected corneal pockets in a baboon model.[42] Medium- and high-water content lenses produced good results without affecting the recipient cornea, whereas thick or low-water content materials extruded or produced severe anterior segment inflammation.

One morphologic study found opacification, vascularization, and chronic inflammation produced by hydrogel corneal lamellar implants,[43] whereas others found no evidence of inflammation.[44,45] Algorithms have been developed to predict the effect of refractive keratoplasty with hydrogel intracorneal implants.[46] The use of medium-and high-water content, convex-shaped lenticles for the correction of aphakia and myopia may be possible using these techniques, if it can be shown that such implants do not interfere with the normal pattern of anterior corneal innervation and nutrition. A new thermoplastic compound termed polysulfone, which has the characteristic of a high refractive index (1.633), shows promise as a material for preparation of intracorneal lenses to correct for high myopia and hyperopia.[47]

New and Developing Areas of Research

Although contact lenses can now be used to treat patients with a wide variety of corneal diseases, many people suffering from other corneal conditions could be helped if they were able to wear contact lenses. New lens designs and materials specifically developed for correction of complex visual anomalies leading to sensory motor dysfunction, such as juvenile aphakia, microphthalmia, and nystagmus are needed. Another challenge is to develop satisfactory contact lenses that will significantly improve the vision of patients suffering from high refractive errors, irregular astigmatism, and anisometropia. Also, more information is needed to understand completely the response of aphakic and myopic eyes to extended contact lenses when they are worn for prolonged periods.

Although keratorefractive surgical procedures may provide important benefits, they may also pose serious risks. Continued National Eye Institute support is required to support the collection of adequate data on the safety and efficacy of these procedures. In particular, appropriate animal models are essential for developing and analyzing the short- and long-term effects of the various refractive corneal surgical procedures before they are applied to large numbers of patients.

Improved utilization of computers will help in developing mathematical models that will assist in patient selection for these surgical procedures. New contact lens materials that could be used for intrastromal implantation should be tested to determine their biocompatibility with the cornea. The efficacy of such surgical techniques as microcollagen shrinkage procedures to modify corneal curvature must be evaluated. New instruments must be developed to permit corneal incisions of predictable depth. Nonradial and circumferential cuts must be evaluated for the correction of astigmatic refractive errors to determine which technique or combination of techniques produces the greater correction with the best predictability.

Refined surgical techniques, such as those employing lasers[48] or new types of surgical blades, are needed to minimize corneal damage. Investigators must assess adjunctive techniques to maintain surgically induced corneal changes, such as the concomitant use of "splint" contact lenses or topical medications[49] after refractive corneal surgery. By improving surgical procedures to simplify corneal lathing[50], eliminating the need for freezing, and otherwise modifying or developing techniques and instrumentation, investigators may be able to make refractive corneal surgery technically easier and available to more patients.

During the past few years, new clinical instrumentation for monitoring corneal and visual changes have been developed, including photoelectric-keratoscopes for measuring corneal contour[51,52], computer-assisted analysis of corneal topography[53], the electronic digital pachymeter for monitoring corneal thickness[54], and the specular microscope for assessing the morphology of the endothelium.[55] Additionally, new instruments such as the fluorophotometer[56], corneal anesthesiometer[57], and oxygen sensor[58] have been designed. The fluorophotometer has been used to study tear flow under contact lenses and examine tear secretion, tear flow rates, and their effect on the cornea.[59] It also has potential use in studying the permeability of the epithelium and endothelium during contact lens wear. In addition, measurements of corneal touch and sensation may prove to be important indicators of changes in corneal physiology.[60] Considerable progress has been made in developing sensors for precisely measuring oxygen uptake by the cornea.[61]

Studies of the mechanical, biosynthetic, and physical factors that allow manipulation of corneal shape are needed. This could be accomplished by the formulation of a finite element model, given the physical characteristics of the corneal stroma and Bowman's membrane. A better understanding of these factors will help in predicting the effectiveness of the various refractive surgical procedures. Additionally, it should be possible to assess which corneas will respond to various modifications and thereby help in defining the eligibility criteria for patients considered for these procedures.

Because many patients undergoing these procedures expect that surgery will improve their vision, they try to convince themselves and the evaluating surgeon that it has. To cope with this subjective bias, it is mandatory to devise a quantitative, objective means to assess visual outcome and complications. In particular, instrumentation and techniques must be designed to monitor objectively the visual and physiological effects of various forms of surgical modification. The long-range effects of surgical modification must be evaluated by carefully designed, randomized controlled clinical trials. The results should be compared with those of conventional methods of correction, such as daily-wear contact lenses, intraocular lenses, and extended-wear contact lenses. Ultimately, the indications for and contra-indications to all surgical procedures that modify the cornea must be defined.

Balance of Effort Within Subprogram

Funding in this subprogram has remained essentially stable over the past several years. New and continuation grants have already been funded in the new and developing areas discussed in Section III, except for human studies of lathing procedures for correction of refractive error, and formulation of a finite element model for the prediction of corneal refractive surgical alterations. Both of these areas, which have recently evolved, will be discussed in Section VI. Relevant research in the areas of contact lens development, epikeratophakia, and Los Alamos electrosurgical keratoplasty procedure, described in Section II, has been supported by private industry during the past several years.

There has been a decline in the Program Base from three grants in FY 1981 to one active grant in FY 1984. The Plan's recommendations are for maintaining funding at this level. There has been a lack of NEI-supported activity in developing new contact lens designs and materials for correction of refractive error (DI), and improving and developing methods for mensuration of optical and physiological properties of the cornea (D4); new insights into these areas are to be sought and encouraged.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

In the Program Base, the evaluation of the safety and efficacy of new procedures and materials for contact lens correction of refractive error (BI), intended as a recommendation to continue ongoing studies of orthokeratology has been accomplished. National Eye Institute-supported study of orthokeratology has shown that although this procedure produces modest reductions in myopia, the effect does not persist without continued lens wear. The studies have been completed and orthokeratology has been found to be a clinically unsatisfactory method for treatment of myopia. Further research support is not warranted.

With regard to the Program Development Priorities, the development of contact lens designs and materials for correction of refractive error (DI) remains important even though no grants have been funded in this category. Major support for this effort were from industry and other private sources.

The Plan's recommendation for Program Development Priority D2 is too general for the broad area of keratorefractive surgical research.

Program Development Priority D3, improve and develop methods for mensuration of optical and physiological properties of the cornea, had no active grants in FY 1984. Present methods are still inadequate and demonstrate the need to increase our knowledge and improve our methods in this area.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends that the existing Program Base category be deleted. Because of the number of research opportunities in the field of research described in Program Development Priority DI, the number of desired grants should be increased. Only one grant was funded in this category in FY 1984. With regard to Priority D2, the Panel recommends that this category be subdiivided into five specific subcategories as follows:

1. Evaluate the safety and efficacy of radial keratotomy in patients.
2. Evaluate the biological effects of radial keratotomy.
3. Develop lathing procedures for surgical correction of refractive error in animals.
4. Study biological effects of intralamellar synthetic implants in the correction of refractive error.
5. Evaluate lathing procedures for surgical correction of refractive error in humans.

Subcategories 1, 2, and 3, as outlined above, have reached an optimal funding level in the context of the overall budget for this subprogram and should now be considered part of the Program Base (B1, B2, and B3). Although additional research is necessary in these areas, the FY 1984 level of funding should be adequate over the next two years.

Although the procedures referred to in subcategories 4 and 5 above may provide important benefits, they may also pose hazards to patients if adequate laboratory and clinical studies are not first performed. It is therefore recommended that new Program Development Priorities be established for the study of biological effects of intralamellar synthetic implants (D2) and for human studies of lathing procedures for correction of refractive error (D3). The Panel recommends an increase in support for Program Development Priority D4 (formerly D3), "improve and develop methods for mensuration of optic and physiologic properties of the cornea."

Studies of the mechanical, biosynthetic, and physical factors that allow manipulation of corneal shape are also needed. This could be accomplished by the formulation of a finite element model for the prediction of corneal refractive surgical alterations. The Panel recommends that a fifth Program Development Priority be established for this purpose.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORRECTION OF REFRACTIVE ERRORS (2-G1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Evaluate safety and efficacy of new procedures and materials for contact lens correction of refractive error. (B1)	3	3	3 [1]	2 [1]	1	3	0	
TOTAL FOR PROGRAM BASE	3	3	3 [1]	2 [1]	1 [0]	3	0	0.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop lens designs/materials for correction of refractive error. (D1)	0	1	0	0	0	4	0	
2. Study biological effects of procedures and materials for surgical or lens correction of refractive error. (D2)	16	20	17 [2]	14	15 [1]	19	5	26.3
3. Improve and develop methods for mensuration of optical and physiological properties of the cornea. (D3)	0	2	0	0	0	2	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	16	23	17 [2]	14 [0]	15 [1]	25	5	20.0
TOTAL FOR SUBPROGRAM	19	26	20 [3]	16 [1]	16 [1]	28	5	17.9
(% OF PROGRAM)	(11.7)	(12.1)	(12.3)	(10.6)	(10.5)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORRECTION OF REFRACTIVE ERRORS (2-G1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Evaluate the safety and efficacy of radial keratotomy in patients. (B1)	NEW (WAS INCLUDED IN OLD D2)	10	0	10	10	10
2. Evaluate the biological effects of radial keratotomy. (B2)	NEW (WAS INCLUDED IN OLD D2)	3	3	0	3	2 [1]
3. Develop lathing procedures for surgical correction of refractive error in animals. (B3)	NEW (WAS INCLUDED IN OLD D2)	2	2	0	1	2
	[DELETED OLD B1]					
TOTAL FOR PROGRAM BASE		15 [0]	5	10	14 [0]	14 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop contact lens designs and materials for correction of refractive error. (D1)	SAME	0 [1]	2	0	1 [2]	1 [2]
2. Study biological effects of intralamellar synthetic implants in the correction of refractive error. (D2)	MORE SPECIFIC	1	2	0	1	1
3. Evaluate lathing procedures for surgical correction of refractive error in humans. (D3)	NEW (WAS INCLUDED IN OLD D2)	0	1	0	0	0
4. Improve and develop methods for mensuration of optic and physiological properties of the cornea. (D4)	SAME (WAS D3)	0	3	0	0 [1]	0
5. Formulate a finite element model for prediction of corneal refractive surgical alteration. (D5)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		1 [1]	9	0	2 [3]	2 [2]
TOTAL FOR SUBPROGRAM		16 [1]	14	10	16 [3]	16 [3]
(% OF PROGRAM)		(10.4)	(6.4)	(50.0)	(9.6)	(9.3)

Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Disease

4

For convenience and easy reference, the Plan divides this subprogram into seven separate areas. The members of the current Panel recommend that Section C, "In Vivo Morphologic Evaluation-Specular Microscopy," which emphasized a developing new technology to evaluate endothelial function and reserve, be eliminated as a separate area and be merged with Section B, "In Vivo Evaluation of Corneal Epithelial and Endothelial Membrane Function." Chapter 4, therefore, is discussed below as the six new sections:

A. Endothelial Tissue Culture, Replacement, and Repair
B. In Vivo Evaluation of Corneal Epithelial and Endothelial Membrane Function
C. Endothelial and Epithelial Transport Processes (Corneal Hydration and Edema)
D. Stromal Swelling and Transparency
E. Normal Corneal Development
F. Corneal Dystrophies, Inherited Disorders, and Developmental Anomalies

Endothelial Tissue Culture, Replacement, and Repair

Perspective on Recent Research

Recent developments in the area of endothelial tissue culture include investigations on elaboration of basement membrane,[1] the roles of growth factors[2-5] and extracellular matrix[6,7] on monolayer organization and cell proliferation, and the augmentation of cell numbers by exogenous cells.[8] It has been shown that endothelium from human corneal rims can be grown in tissue culture.[9] It has also been possible to transplant endothelial cells from tissue culture back into animal eyes to produce a return of normal clarity.[10,11] However, complications have been encountered, most notably that of immunologic rejection of the transplanted endothelium. Also, evidence has been provided for growth factor receptors on corneal endothelium[14] and that growth factors can stimulate endothelial wound repair in organ culture systems[15,16] and in vivo.[17]

Progress in Areas Discussed in the 1983-1987 Plan

Major accomplishments over the past several years in the area of endothelial tissue culture include investigation of the roles of various growth factors on monolayer organization,[5] cell proliferation,[2,4] and differentation.[3] The extracellular matrix has been shown to play an important role in endothelial cell growth and culture longevity.[6,7] In vitro elaboration and organization of basement membrane has been detailed. Successful in vitro growth of human corneal endothelium derived from corneal scleral rims obtained following corneal transplantation has been reported.[9] It has been demonstrated that the number of corneal endothelial cells in culture is strictly regulated but may be augmented by exogenous cells.[8]

Evidence for growth factor receptors on feline and human corneal endothelium has been demonstrated.[14] Also, growth factors have been found to stimulate endothelial cell repair in vitro[15,16] and in vivo.[17] Another significant advance is the successful transplantation of tissue cultured corneal endothelium[11-13] and vascular endothelium[18] in animals, resulting in a return of normal endothelial physiological function, morphology, and normal corneal clarity. However, complications have been encountered, most notably that of immunologic rejection of the heterologous transplanted endothelium, a problem that must be elucidated.[12,13] Because a species variability of the corneal endothelium has been found in vivo and in vitro,[19] it is necessary to choose animal models for research that most closely approximate the human condition so that better approaches can be developed to endothelial replacement and repair in man.[20,21]

New and Developing Areas of Research

Evaluation of the growth of endothelial cells in culture, including media requirements, supplements, growth factors, substrate requirements, interactions, and species variability is needed. The characteristics of tissue-cultured corneal endothelium from normals—both animals and man—with particular attention to the aging characteristics of these cells and the affect of age on in vitro characteristics need to be determined, as do their in vitro physiological capabilities and biosynthetic characteristics.

Recent experiments have demonstrated that corneal transplants bearing cultured homologous[10] or heterologous[11-13] corneal endothelial cells become clear and appear to function normally. These experiments have important clinical implications because the ability to use cultured corneal endothelial cells to repopulate corneal surfaces prior to penetrating keratoplasty would increase the number of corneas suitable for transplantation as well as provide a means of standardizing the endothelial population of donor preparations.

However, in recent experiments,[12,13] clinical, morphologic, and immunologic evaluation of the transplants demonstrated a host response directed against the grafted heterologous endothelium, a complication not previously noted. These experiments suggest that the use of cultured heterologous endothelial cells in corneal transplantation may have significant dangers as well as potential benefits. The recipient response to corneal homografts relined with heterologous corneal endothelium must be closely investigated and controlled for the transplanted cells to survive postoperatively. Investigations must include immune mediated phenomena in the local area of the transplant (aqueous humor or anterior chamber) as well as systemic responses.

The role of tissue cultured corneal transplantation, and the value of mixed lymphocyte response in predicting the successful outcome of impending corneal transplantation must now be investigated. Also, studies utilizing autologous endothelial cells from sources such as blood vessels are required.

Further evaluation of in vivo stimulation of native endothelial repair and restoration of function is necessary. Which growth factors are the most appropriate for this use, and how and when to deliver them must be determined. Endothelial growth receptors need to be characterized.

Balance of Effort Within Subprogram

The number of grants funded in this area in FY 1984 increased slightly since FY 1981 and actually achieved the Plan's recommendation of seven grants in FY 1983. It is also noteworthy that new and continuation grants have already been funded in the new and developing areas discussed in Section III.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Program Base category specified in the Plan, B1, continues to be a relevant category of research. Although both of the Program Development Priorities continue to be relevant, funding in Priority DI has nearly reached an optimal level in the context of the overall budget.

Recommended Changes in Program Base and/or Program Development Priorities

For the reason cited above, Priority DI should now be considered part of the Program Base. Although additional research is necessary in this category, as outlined earlier, the funding of one additional project should be adequate.

The remaining Program Development Priority, D2, should be expanded to include research on methods of restoring function to, as well as stimulating repair of, corneal endothelium in vivo and one additional grant should be funded in this area as well.

In Vivo Evaluation of Corneal Membrane Function

Perspective on Recent Research

Some progress has been made in this area since the Plan was published, much of which suggests that novel approaches need be applied in this area of research. Although the corneal endothelium cannot in general replenish cells lost through aging and trauma, recent studies support the notion that as long as the remaining cells are able to cover the inner corneal surface by migration and/or enlargement, stromal hydration and clarity can be maintained. A corneal stress test has been used, as suggested in the Plan, and, given the normal functional reserve of the endothelium, such tests may offer the best promise for evaluating endothelial functional reserve in vivo.

With regard to corneal thickness measurement, a new tool has been reported which may lead to methods for the assessment of corneal thickness profiles over the entire corneal surface.[22]

Progress in Areas Discussed in the 1983-1987 Plan

In previous studies, very little correlation had been found between endothelial cell density and corneal thickness. Recently, researchers have similarly found no correlation between endothelial cell fluorescein permeability and either age, intraocular pressure, or volume of the anterior chamber.[23] On the other hand, it has been shown that in patients with corneal guttata (early Fuchs' dystrophy), endothelial permeability to fluorescein increases with increasing cell size.[24] This contrasts with the observation that endothelial permeability in corneal transplants is less than that of normals.[25] It is well established that endothelial cell density in corneal transplants is markedly reduced. It was proposed that, inasmuch as fluorescein is an extracellular marker passing between endothelial cells, in the case of Fuchs' dystrophy, junctions between the corneal endothelial cells are rendered more permeable. However, in the case of corneal transplants with enlargement of endothelial cells, there is less available corneal surface area for the permeation of fluorescein. Hence, despite the variability observed in the measurement of corneal endothelial fluorescein permeability,[23] the use of the ophthalmic fluorophotometer appears to be helpful for studying the etiology of corneal endothelial dysfunction.

Still, the question remains: what is the functional reserve of a given patient's cornea, and what are the chances for its decompensation following various intraocular surgical procedures? Because the corneal endothelium ordinarily has a tremendous functional reserve, more needs to be learned about the functioning of the cornea, that has been stressed by intraocular surgery, corneal refractive surgery, and contact lens wear.

New and Developing Areas of Research

Stress tests were proposed in the Plan. In one study, contact lenses were used to induce corneal edema. The speed with which the cornea recovered was found to be related to patient age.[26] However, the extent of the hypoxic stress induced by contact lenses depends on several factors, such as individual fit, which leads to a certain variability in the results. Nevertheless, with improvement, stress tests may provide a reliable indicator of functional reserve in the corneal endothelium.

The Plan specified the need to develop an inexpensive, easy to use specular microscope with a large field of view and an optical scanning device to enable rapid, direct computer analysis of cell counts and morphology. This need has been largely met by industrial efforts and, therefore, should be deemphasized for NEI support.

Balance of Effort Within Subprogram

Funding in this area has declined from a total of five grants in FY 1981 (in both the "In Vivo Evaluation of Corneal Epithelial and Endothelial Membrane Function" and the "In Vivo Morphologic Evaluation —Specular Microscopy" areas) to three projects in FY 1984. However, there were several Corneal Diseases projects funded in FY 1984 that are generally concerned with the broad objective of these subprogram areas, but are categorized elsewhere. Hence, significant emphasis is being given to this important area of corneal research.

Traditionally, applications for research support, that focus on the development of technology per se do not fare well in the grants review process despite the emphasis given such projects in this section of the Plan. As noted above, some attention to the goals specified in this chapter has been forthcoming from the commercial sector, and the funding burden on NEI has thereby been reduced.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Plan's statement of need for better methods to evaluate corneal membrane function in vivo remains a high priority. This area of the NEI Corneal Diseases program represents the important extension of in vitro and animal model work to human medical problems. The Plan also specified two research needs relating to specular microscopy: correlation of endothelial morphology with physiological function and with histopathology. These should be condensed to a single statement of need: correlation of morphologic appearance under the specular microscope with endothelial cell function and dysfunction.

Recommended Changes in Program Base and/or Program Development Priorities

In addition to its recommendation to incorporate area C (In Vivo Morphologic Evaluation—Specular Microscopy) of this subprogram into this section, the Panel recommends that the Program Base and Program Development Priorities be revised. The Program Base category from area C should be transferred to the Program Base of this section and re-worded to emphasize the development of methods. An additional grant should be funded in this category. The original Program Base category (BI) from this section should be combined with the Program Development Priority into a single recommendation, and one additional grant should be funded for this recommendation.

Endothelial and Epithelial Transport Processes (Corneal Hydration and Edema)

Perspective on Recent Research

Recent developments in this area have mainly been the result of fundamental observations of cell mechanisms involved in corneal epithelial and endothelial transport processes, which are the basis for the control of corneal edema and transparency. New tools have been applied to study these processes at the membrane level, and significant strides have been made in understanding the role of corneal innervation in the modulation of corneal function.

Progress in Areas Discussed in the 1983-1987 Plan

The techniques of membrane patch clamping, wherein a small area of cell lipid bilayer membrane is isolated for study, have been successfully applied to the study of the corneal endothelial pump.[27] Specific membrane ion channels are being characterized with the aim of gaining sufficient insight into the mechanisms by which the endothelial cells control edema so that this important function might be improved.

Two new hormone receptors have been identified in the cornea which are specific to serotonin[28-30] and one of which is specific to dopamine.[31] Both receptors appear to play a role in corneal epithelial transport processes and their action depends upon normal innervation by the sympathetic nervous system. These studies should provide a better understanding of the interaction of corneal nerves with the maintenance of normal corneal cell metabolism.

New and Developing Areas of Research

The application of the membrane patch clamp technique holds great promise for the future understanding of corneal endothelial transport processes. In the area of corneal cell metabolism, powerful lipid biochemistry technology is being used to explore the role of cell and membrane lipid metabolism in corneal layer functional properties.[32] The growing availability of powerful microcomputer technology will make possible significant advances in many areas of study within this field. Several recent grants funded in this area have made major progress in research areas which had been avoided in the past because of the extraordinary cost which had been associated with large-scale computer use.

Balance of Effort Within Subprogram

This subprogram area is the part of the NEI Corneal Diseases program where it is mostly likely that major fundamental advances in the study of corneal function might be made. NEI-supported projects in this area have provided the basis of current understanding of corneal function as well as the springboard for applied research in other sections of the program.

Since FY 1981, overall funding has increased in this area, from 10 grants in FY 1981 to 16 in FY 1984. However, much of the increase occurred in the Program Base in which no growth was projected in the Plan. The increase of funding in Base has been the result of the identification of new hormone receptor sites not previously anticipated. However, grants have also been awarded for research in the new and developing areas discussed above.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Plan's recommendations for research in this area continue to be relevant and, as stated above, can encompass the new research opportunities.

Recommended Changes in Program Base and/or Program Development Priorities

Because of the increase in research activity since the Plan was published in studying the neural and hormonal factors that influence metabolism of epithelial and endothelial layers, due to the new research opportunities in this field, the Panel recommends changing this Program Base category (BI) to a Program Development Priority with an increase of two additional grants above the FY 1984 level. Conversely, because research in Priority DI would be at an adequate level of activity if it achieved the 11 grants originally recommended in the Plan, it should now be categorized as part of the Program Base with a continued recommendation of 11 grants. New Program Development Priorities need not be specified because the aims of the currently funded grants are such that when new technologies become available, these can be utilized to accomplish previously stated goals.

Stromal Swelling and Transparency

Perspective on Recent Research

Irreversible opacification of the corneal stroma can be successfully corrected in many patients with a full thickness corneal transplant. The causes of stromal opacification can be divided into two separate categories: edema, caused by endothelial disorders, and inclusion disorders. In the former condition, the stroma is altered solely by swelling, which leads to a disruption of the normal arrangement of the collagen fibers. Edema produces a general increase in stromal light scatter and can be sufficient reason by itself for an ophthalmologist to recommend a corneal transplant to replace the dysfunctional endothelial cells. Inclusion disorders occur from stromal dystrophies, neovascularization, and scarring. Both categories of corneal opacification are addressed by the research needs expressed in this section.

Work in this area has progressed satisfactorily since the writing of the Plan.

Progress in Areas Discussed in the 1983-1987 Plan

Progress continues to be made in research on the theory of corneal stromal transparency[33] Although the underlying principles of transparency in the corneal stroma are fairly well understood, it is important to devise calculational methods that can be used to evaluate the light scattering caused by corneal scars such as those produced in the radial keratotomy procedure.[34] Recently, the role of retinoids in the biosynthetic capabilities of stromal keratocytes was examined in tissue culture.[35] In this work, retinoids were shown to increase the synthesis of extracellular matrix substances, notably glycosaminoglycans and fibronectin.

New and Developing Areas of Research

Pilot studies in several laboratories in the United States are currently underway to determine the mechanical properties of Bowman's layer, stroma, and Descemet's membrane in mammals. These data will be used as the basis of computer models in conjunction with the needs for predictive methods and corneal refractive surgical procedures.

Balance of Effort Within Subprogram

In FY 1984, five grants were funded in this area, three fewer than called for by the Plan. In particular, the Panel was concerned that only one grant was awarded in FY 1984 Program Base category B2, in which there were 4 grants in FY 1981 and expressed its belief that more emphasis is needed here.

Adequacy and Current Relevance of the Program Base

The Panel believes that the Plan's recommendations for this area continue to be adequate.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends adding additional grants to study light transmissibility of the stroma and to develop techniques to measure changes with disease and increased hydration (B2). No other changes are recommended in this area, nor is there any reason to designate Program Development Priorities.

Normal Corneal Development

Perspective on Recent Research

Since publication of the Plan, advances in cell culture and monoclonal antibody techniques have been made and applied to this area of research. These suggest new opportunities for research in this area that were not possible when the Plan was drafted.

Progress in Areas Discussed in the 1983-1987 Plan

Great advances have been made in the biochemical characterization as well as the in vitro reconstitution of basement membrane.[36-38] Advances have also been made in understanding the interaction of embryonic corneal epithelium with extracellular matrix components,[39-41] and hemidesmosome formation.[42] The collagens synthesized during corneal development have been further characterized.[43]

New and Developing Areas of Research

Monoclonal antibodies to various corneal cell types as well as a 64K-corneal specific epithelial keratin[44-46] have recently become available; these antibodies can be expected to generate useful information about corneal development. Cell culture techniques of all three major corneal cell types (epithelial, fibroblast and endothelial) have been further improved, allowing detailed in vitro analysis of corneal cell growth and differentation.

Balance of Effort Within Subprogram

The Plan recommended that funding in this area continue at the FY 1981 level of two grants and two were funded in FY 1984, although four grants were active in FY 1982-3.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Program Base category continues to be relevant. In addition, because of the development of the cell culture and monoclonal antibody techniques discussed above, there are now several new opportunities for significant program development in this area.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends that the Program Base remain the same and two new Program Development Priorities be added:

1. Define normal corneal development using modern technologies including monoclonal antibodies and gene cloning.
2. Investigate the roles of corneal cell-matrix interaction during normal corneal development and differentation.

Corneal Dystrophies, Inherited Disorders, and Developmental Anomalies

Perspective on Recent Research

Corneal dystrophies continue to pose significant problems in the maintenance of corneal clarity and eye comfort. The endothelium must be assessed in preparation for any type of intraocular surgery and responds to any type of corneal surgery and contact lens wear. Dystrophic endothelium and dystrophies or inherited diseases affecting any of the other principal layers and cells predispose the cornea to development of edema, recurrent erosive disorders, and decreased vision. The recognition of endothelial dystrophy has improved considerably with the development of endothelial specular microscopy and pachometry. Clinical experience and correlation of surgical results with such measurements is still being gained. Compensatory mechanisms are now being realized and the physiologic effect of morphologic findings are gaining greater appreciation.

Progress in Areas Discussed in the 1983-1987 Plan

Pump function of the human corneal endothelium may improve with an increase in pump site density in the presence of moderate guttata.[47] Cytochemical localization of pump activity was carried out in human corneal buttons of Fuchs' dystrophic corneas by measuring Na-K-ATPase activity, which appeared reduced.[48] Severe guttata does appear to be associated with endothelial dysfunction as indicated by pachometry demonstrating an average 25% increase in corneal thickness (0.542 to 0.679) in a group of 14 eyes whose guttata progressed from moderate to severe guttata over a five year period.[49]

New and Developing Areas of Research

A monoclonal antibody (ET-4A4) that recognizes keratan sulfate, derived from skeletal and corneal tissues, has been used to develop an ELISA (enzyme linked immunosorbent assay) to quantify the sulphated polysaccharide.[50] Significant amounts of keratan sulphate have been found in the sera of a large study group of hospitalized patients, but the compound was not detected in the sera of nine patients with a clear diagnosis of macular corneal dystrophy. Because keratan sulphate has been observed in the blood of normal newborns, this new assay should allow diagnosis of the dystrophy at birth, long before clinical symptoms appear.

Corneal endothelial cell density has been determined as a function of donor age for 20 pairs of donor corneas having normal endothelia.[47] In this group of donor corneas, a significant negative correlation was found between donor age and central cell density: predicted cell density = 3384 cells/mm^2—10.7 (donor age).

In contrast to this decrease in cell density with increasing age, the amount of ouabain bound to the tissue layer, and hence the density of Na/K ATPase pump sites, was found to remain constant and to be independent of age. These data demonstrate that as endothelial cells are lost, the remaining cells adapt to the loss by generating new pump sites in order to maintain normal pump and barrier functions.

Balance of Effort Within Subprogram

The single Program Base category in this section is to "Establish a national registry of corneal dystrophies." Such a registry of macular corneal dystrophy has been established as part of a broader study of pathogenetic factors in corneal vascularization and basic biochemical defects in corneal dystrophies.

The determination of abnormal products in dystrophic corneas (D1) seems to have stabilized at an appropriate level of activity, while the identification of basic mechanisms for the development of corneal dystrophies (D2) and the study and search for animal models of corneal dystrophies (D3) should be brought to the levels recommended in the Plan.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

Because there is no need to duplicate the corneal dystrophy registry, which continues to be funded as part of a grant to identify basic mechanisms responsible for development of corneal dystrophies (D2), the Panel recommends deleting it as a separate research category.

Although none of the Program Development Priorities achieved the levels recommended in the Plan, they continue to be relevant and important areas of research.

Recommended Changes in Program Base and or Program Development Priorities

The Panel recommends, as noted above, deleting Program Base category B1. Furthermore, the Panel recommends specifying in Program Development Priority D1 the inclusion of corneas from in situ sources and organ and tissue culture and moving it to the Program Base because it is at an appropriate level of activity. The remaining Program Development Priorities should be increased by an additional grant each to bring them to the levels recommended in the Plan.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: ENDTH. TISSUE CULTURE, REPLACEMENT, REPAIR (2-H2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Evaluate in vitro biosynthetic and physiologic characteristics of normal and diseased corneal endothelium. (B1)	3	3	1	3 [1]	3	5	4	80.0
TOTAL FOR PROGRAM BASE	3	3	1 [0]	3 [1]	3 [0]	5	4	80.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Define in vitro needs of corneal endothelium in tissue culture and develop techniques for transplantation in man. (D1)	1	3	2	2	1 [1]	4	1	25.0
2. Develop methods to stimulate repair of corneal endothelium in vivo. (D2)	1	1	2	2 [1]	2	4	1	25.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	2	4	4 [0]	4 [1]	3 [1]	8	2	25.0
TOTAL FOR SUBPROGRAM	5	7	5 [0]	7 [2]	6 [1]	13	6	46.2
(% OF PROGRAM)	(3.1)	(3.2)	(3.1)	(4.6)	(3.9)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: ENDTH. TISSUE CULTURE, REPLACEMENT, REPAIR (2-H2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Evaluate in vitro biosynthetic and physiologic characteristics of normal and diseased corneal endothelium. (B1)	SAME	3	3	0	4	3 [1]
2. Define in vitro needs of corneal endothelium in tissue culture and develop techniques for transplanting tissue-cultured corneal endothelium in man. (B2)	MOVED, MORE SPECIFIC (WAS D1)	1 [1]	2	0	1 [1]	1 [1]
TOTAL FOR PROGRAM BASE		4 [1]	5	0	5 [1]	4 [2]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop methods to stimulate repair and restore function of native corneal endothelium in vivo. (D1)	EXPANDED, LESS SPECIFIC (WAS D2)	2	3	0	2	3
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	3	0	2 [0]	3 [0]
TOTAL FOR SUBPROGRAM		6 [1]	8	0	7 [1]	7 [2]
(% OF PROGRAM)		(3.9)	(3.7)	(0.0)	(4.2)	(4.1)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: IN VIVO EVALUATION OF CORNEAL MEMBRANE FUNCTION (2-H3)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Develop methods for in vivo assessment of epithelial and endothelial barrier function. (B1)	2	2	1	1	1	0	0	
TOTAL FOR PROGRAM BASE	2	2	1 [0]	1 [0]	1 [0]	0	0	0.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop methods for in vivo assessment of epithelial and endothelial metabolic function. (D1)	1	3	1	1 [1]	1	4	1	25.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	3	1 [0]	1 [1]	1 [0]	4	1	25.0
TOTAL FOR SUBPROGRAM	3	5	2 [0]	2 [1]	2 [0]	4	1	25.0
(% OF PROGRAM)	(1.8)	(2.3)	(1.2)	(1.3)	(1.3)			

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: IN VIVO MORPH. EVALUATION--SPECULAR MICROSCOPY (2-H4)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Correlate morphologic appearance with physiologic function and reserve. (B1)	2	3	2	1	1	0	0	
TOTAL FOR PROGRAM BASE	2	3	2 [0]	1 [0]	1 [0]	0	0	0.0
TOTAL FOR SUBPROGRAM	2	3	2 [0]	1 [0]	1 [0]	0	0	0.0
(% OF PROGRAM)	(1.2)	(1.4)	(1.2)	(0.7)	(0.7)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: IN VIVO EVALUATION OF CORNEAL MEMBRANE FUNCTION (2-H3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No R03, R43, R44]
PROGRAM BASE						
1. Develop methods to correlate morphological appearance with physiological function and reserve. (B1)	MOVED, MORE SPECIFIC (WAS 2-H4, B1)	1	2	0	3	3
TOTAL FOR PROGRAM BASE		1 [0]	2	0	3 [0]	3 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop methods for in vivo assessment of epithelial and endothelial function. (D1)	MOVED, LESS SPECIFIC (COMBINES OLD B1 AND D1)	2	3	0	4	3 [1]
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	3	0	4 [0]	3 [1]
TOTAL FOR SUBPROGRAM		3 [0]	5	0	7 [0]	6 [1]
(% OF PROGRAM)		(1.9)	(2.3)	(0.0)	(4.2)	(3.5)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNC./DYSTROPHIES/INHERITED DISEASES: ENDOTH./EPITH. TRANSPORT PROCESSES (HYDRATION/ EDEMA) (2-H5)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Evaluate neural and hormonal factors that influence metabolism of epithelial and endothelial layers. (B1)	1	1	1 [2]	5	5	5	4	80.0
TOTAL FOR PROGRAM BASE	1	1	1 [2]	5 [0]	5 [0]	5	4	80.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Compare membrane metabolic function of normal and diseased corneas from animals and man. (D1)	9	11	9	9	9	7	6	85.7
2. Determine nutritional needs of corneal endothelium and endothelial influences on stromal and epithelial metabolism. (D2)	0	1	1	2	2	4	2	50.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	9	12	10 [0]	11 [0]	11 [0]	11	8	72.7
TOTAL FOR SUBPROGRAM	10	13	11 [2]	16 [0]	16 [0]	16	12	75.0
(% OF PROGRAM)	(6.2)	(6.3)	(6.7)	(10.6)	(10.5)			

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: STROMAL SWELLING AND TRANSPARENCY (2-H6)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Evaluate stromal biochemical changes with disease and aging. (B1)	3	3	4	4	4	6	1	16.7
2. Study light transmissibility of stroma and develop techniques to measure changes with disease and increased hydration. (B2)	4	5	2	1	1	2	0	
TOTAL FOR PROGRAM BASE	7	8	6 [0]	5 [0]	5 [0]	8	1	12.5
TOTAL FOR SUBPROGRAM	7	8	6 [0]	5 [0]	5 [0]	8	1	12.5
(% OF PROGRAM)	(4.3)	(3.7)	(3.7)	(3.3)	(3.3)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNC./DYSTROPHIES/INHERITED DISEASES: ENDOTH./EPITH. TRANSPORT PROCESSES (HYDRATION/ EDEMA) (2-H5)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Compare membrane metabolic function of normal and diseased corneas from animals and man. (B1)	MOVED (WAS D1)	10	11	0	8	10 [1]
TOTAL FOR PROGRAM BASE		10 [0]	11	0	8 [0]	10 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Evaluate neural and hormonal factors that influence metabolism of epithelial and endothelial layers. (D1)	MOVED (WAS B1)	3	7	0	4	4
2. Determine nutritional needs of corneal endothelium and endothelial influences on stromal and epithelial metabolism. (D2)	SAME	2	2	0	2	2
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		5 [0]	9	0	6 [0]	6 [0]
TOTAL FOR SUBPROGRAM		15 [0]	20	0	14 [0]	16 [1]
(% OF PROGRAM)		(9.7)	(9.3)	(0.0)	(8.4)	(9.3)

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: STROMAL SWELLING AND TRANSPARENCY (2-H6)

PROGRAM BASE						
1. Evaluate stromal biochemical changes with disease and aging. (B1)	SAME	4	4	0	5	4 [1]
2. Study light transmissibility of stroma and develop techniques to measure changes with disease and increased hydration. (B2).	SAME	1	3	0	1	2
TOTAL FOR PROGRAM BASE		5 [0]	7	0	6 [0]	6 [1]
TOTAL FOR SUBPROGRAM		5 [0]	7	0	6 [0]	6 [1]
(% OF PROGRAM)		(3.2)	(3.2)	(0.0)	(3.6)	(3.5)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: NORMAL CORNEAL DEVELOPMENT (2-H7)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Analyze effect of cellular differentiation on corneal morphogenesis and biochemical composition. (B1)	2	2	4	4	2	5	2	40.0
TOTAL FOR PROGRAM BASE	2	2	4 [0]	4 [0]	2 [0]	5	2	40.0
TOTAL FOR SUBPROGRAM	2	2	4 [0]	4 [0]	2 [0]	5	2	40.0
(% OF PROGRAM)	(1.2)	(0.9)	(2.5)	(2.6)	(1.3)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: NORMAL CORNEAL DEVELOPMENT (2-H7)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Analyze effect of cellular differentiation on corneal morphogenesis and biochemical composition. (B1)	SAME	2	2	0	2	2
TOTAL FOR PROGRAM BASE		2 [0]	2	0	2 [0]	2 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Define normal corneal development using modern technologies including monoclonal antibodies and gene cloning. (D1)	NEW	2	4	0	0	1
2. Investigate the roles of corneal cell matrix interaction during normal corneal development and differentiation. (D2)	NEW	0	2	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	6	0	0 [0]	1 [0]
TOTAL FOR SUBPROGRAM		4 [0]	8	0	2 [0]	3 [0]
(% OF PROGRAM)		(2.6)	(3.7)	(0.0)	(1.2)	(1.7)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: DYSTROPHIES/INHERITED DISORDERS/DEVELOP. ANOMALIES (2-H8)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Establish national registry of corneal dystrophies. (B1)	1	1	1	1	1	0	0	
TOTAL FOR PROGRAM BASE	1	1	1 [0]	1 [0]	1 [0]	0	0	0.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Determine abnormal products in dystrophic corneas. (D1)	2	3	2	2	1	1	0	
2. Identify basic mechanisms responsible for development of corneal dystrophies. (D2)	1	2	1	0	0	0	0	
3. Study and search for animal models of corneal dystrophies. (D3)	0	1	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	3	6	3 [0]	2 [0]	1 [0]	1	0	0.0
TOTAL FOR SUBPROGRAM	4	7	4 [0]	3 [0]	2 [0]	1	0	0.0
(% OF PROGRAM)	(2.5)	(3.2)	(2.4)	(2.0)	(1.3)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL EDEMA/ENDOTHELIAL DYSFUNCTION/DYSTROPHIES/INHERITED DISEASES: DYSTROPHIES/INHERITED DISORDERS/DEVELOP. ANOMALIES (2-HB)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Determine abnormal products in dystrophic corneas, corneas from in situ sources, and after organ or tissue culture. (B1)	MOVED, MORE SPECIFIC (WAS D1)	1	1	0	0	0
	[DELETED OLD B1]					
TOTAL FOR PROGRAM BASE		1 [0]	1	0	0 [0]	0 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Identify basic mechanisms responsible for development of corneal dystrophies. (D1)	SAME (WAS D2)	1	2	0	1	1
2. Study and search for animal models of corneal dystrophies. (D2)	SAME (WAS D3)	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		1 [0]	3	0	1 [0]	1 [0]
ADDITIONAL RESEARCH CATEGORIES						
1. Other. (A1)		0	0	0	0 [1]	0
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES		0 [0]	0	0	0 [1]	0 [0]
TOTAL FOR SUBPROGRAM		2 [0]	4	0	1 [1]	1 [0]
(% OF PROGRAM)		(1.3)	(1.8)	(0.0)	(0.6)	(0.6)

Corneal Transplantation and Stromal Wound Healing

5

Perspective on Recent Research

A. Inflammation and Repair

Studies in this area have focused on the role of collagenolytic activity of inflammatory cells in the process of corneal stromal ulceration and the role of immune phenomena in conjunctival inflamation and corneal vascularization. There has been relatively little achieved in the other areas which are emphasized in the Plan. In part, this slow progress is attributable to the technical difficulties in the one of the Program Base activities, the development of sensitive methods for analyzing minute quantities of corneal matrix materials (B5).

B. Corneal Transplantation

Study of the role of antigens in the initiation of the corneal graft immune reaction continues to occupy both basic and clinical scientists. There is now increasing evidence that class II MHC antigens are found in all three layers of the cornea.[1-3] In addition, gamma interferon can induce the expression of class II antigen on endothelial cells.[4-6] Host recognition may be the result of passenger leukocytes such as dendritic Langerhans cells plus corneal endothelial cells expressing class II antigens following exposure to gamma interferon, serving as the effector portion of the rejection.[7-10] The clinical importance of HLA tissue typing continues to be investigated, with a multicenter investigation now underway. The use of cyclosporine has become standard therapy for prevention of solid organ graft rejection. Newly initiated studies of the effectiveness of this therapy in high-risk cases of corneal transplantation are now underway to evaluate the risk/benefit ratios in such patients.

Clinicians have given considerable attention to the prevention of high degrees of corneal astigmatism. The role of corneal graft position has been evaluated in some clinical studies, which suggest that astigmatism can be anticipated and controlled by varying the location of the donor transplant in the host cornea.[11,12] Selective removal of sutures has also been advocated as a method for controlling the refractive result of keratoplasty.[13]

Progress in Areas Discussed in the 1983-1987 Plan

A. Inflammation and Repair

The role of collagenolytic activity of inflammatory cells in the process of corneal stromal ulceration has been examined. These cells, particularly polymorphonuclear leukocytes, have been found to be an important source of collagenase,[14,15] and their presence has been linked to the corneal ulceration characteristic of chemical injury and infectious processes. The cascade of events that ultimately leads to collagen destruction continues to be elucidated.[16,17] To date, however, no new therapeutic approaches have resulted from these investigations.

The role of immune complexes and other immune phenomena in the initiation of conjunctival inflammation and peripheral corneal ulceration continues to yield important information. Mediators such as the leukotrienes have been implicated in the initiation of conjunctival scarring.[18]

Corneal vascularization has been characterized as a component of acute inflammation, and numerous studies have attempted to elucidate its pathogenesis. Recent work has focused on the role of effects of T-cells in angiogenesis.[19] In rabbits, activated T-cells produce angiogenic lymphokines. Likewise, murine effector T-cells produce materials that are angiogenic, and the production of these materials is associated with I-region alloantigens.[20] The inhibition of vascularization was achieved by the use of heparin-cortisone-impregnated cellulose acetate pellets.[21] This was recently applied to inhibit vascularization in vascularized rabbit corneas.[22] The vascularization from the host into the graft was avoided for 6 weeks, a period thought sufficient to be useful during the initial critical period of stromal wound healing.

More direct approaches to reduce stromal vascularization have involved laser treatment of vascular loops that encroach on the cornea.[23] Although these studies are not yet complete, there is evidence in some cases that interruption of the blood flow leads to regression of the vessels and of attendant corneal lipid deposition.

The role of stromal repair in the production of corneal warping and astigmatism has assumed great significance with the rapid increase in the frequency of refractive surgery. The continued change in refractive error that accompanies many radial keratotomy procedures[24] is an example of the slow and apparently unpredictable change in corneal curvature that follows the deep radial incisions. The cellular mechanism responsible for tissue repair and remodeling continues to be explored,[25] and it is expected that these new surgical procedures will re-emphasize the importance of these studies.

B. Corneal Transplantation

There has been considerable activity in the Program Base category BI of exploring the usefulness of biopolymers for insertion into the cornea to alter its refraction. This has been investigated in at least two laboratories.[26,27] Initial problems with predictability of the final curvature appear to be solved, so that investigation of the use of these intrastromal lenticules in humans can now proceed. The greatest amount of clinical activity in this area has tended to cut across the fields of corneal transplantation, wound healing, and control of postoperative refraction and astigmatism. Continued large-scale research activity in exploring potential applications for epikeratophakia have brought to attention the problem of re-epithelialization of lathed lenticules of stroma-containing non-viable keratocytes.[28,29] The absence of immune reaction to transplanted stromal lenticules raises questions about the potential for stroma to serve as an antigen, despite the presence of cell surface antigens on the keratocytes.

The Program Development Priorities have received considerable attention also. The importance of tissue typing and tissue-specific antigens (Dl) has been addressed by at least one clinical study[30] and is currently the subject of a multicenter evaluation of the utility of HLA-DR matching in high-risk cases. Most observers agree that tissue typing is not necessary in low-risk cases, because success rates are high regardless of the compatibility of the tissue used.[31]

The immunological control mechanisms that might be used to reduce the frequency and severity of graft reactions (D2) are now being studied for corneal tissue.[32] Reduction of initial host sensitization would be highly desirable, because it would reduce the need for frequent high-dose corticosteroids to combat each rejection episode.

Another highly important Program Development Priority is that of testing new drugs that have the potential for modifying or eliminating the allograft reaction(D3). The prototypical drug for this purpose is cyclosporine whose use has now become standard in renal, liver, and heart transplantation. Experience is now being gained in the use of this medication for uveitis (see *Report of the Retinal and Choroidal Diseases Panel*) and a clinical trial of this medication for high-risk corneal transplants is underway.

The mechanism of post-transplant complications (D5) such as endothelial failure, glaucoma, astigmatism, and cystoid macular edema (CME) are being studied, primarily by observations made in large series of clinical cases.[33,34] There has been little use of animal models for this work except in the case of radial keratotomy, where owl monkey eyes have been found to react similarly to human eyes.[35] Monkeys have also been used to study the effect of radial keratotomy on the number and configuration of endothelial cells.[36]

New and Developing Areas of Research

A. Inflammation and Repair

The role of inflammatory mediators such as the leukotrienes in stromal ulceration and subsequent tissue repair appears to be a contemporary research interest that should now be applicable to corneal research. Further elaboration of the "cascade" effect of mediators such as plasminogen-activator[4] and alpha-2 macroglobulin should now be possible.

The basis for the immunologically mediated stromal swelling seen in herpetic disease should be investigated. There is now considerable evidence to suggest that the rate of endothelial cell water transport is under active control and is therefore variable. It seems likely that some product of the host immunologic reaction has a direct adverse effect on the function of the endothelial cells, rendering them less competent in fluid transport. The recently reported positive effect of corticosteroids on reducing corneal thickness in healing freeze-injured corneal endothelium suggests that there may be a direct corticosteroid effect on endothelial function, as well as an indirect one on inflammatory cells and their products.

The presence of inflammatory mediators in the stroma of tissue excised at surgery can be evaluated by cultivation of endothelial cells, keratocytes, and inflammatory cells themselves in the presence of extracts from such tissue.[37] Determining the relative role of direct tissue destruction and inhibition of synthesis should be possible in corneal tissue as it has been in other types of tissue necrosis.

The recent identification of angiogenin, a mediator produced by cells and responsible for blood vessel growth in at least some tissues[38], should kindle renewed interest in the subject of corneal vascularization. Although control of corneal vascularization by heparin-cortisone and other inhibitors of the previously described tumor-angiogenesis factor (TAF)[8] has been of only peripheral interest to ophthalmologists, the use of such inhibitors and the determination of the role of angiogenesis can now be undertaken in a variety of inflammatory models.[9] Such studies will have a high degree of relevance to such clinical problems as chemical injury, the vascularization seen with trauma after corneal resurfacing from the conjunctiva, and vascularization seen in allograft reaction. Vascularization and its control also cuts across several other areas of ophthalmic research, including neovascular glaucoma and retinal vascular abnormalities, including diabetic retinopathy.

B. Corneal Transplantation

The control of immunologic rejection of corneal tissue remains the central concern of scientists and clinicians concerned with corneal transplantation. As clinical studies produce reliable data regarding the relative risk of graft reaction in a variety of clinical situations, three different approaches can be taken to reduce the loss of technically successful transplants. These include tissue-typing to achieve better matches of host-tissue antigenic determinants, short and long-term control of vascularization to inhibit both the recognition and effector arms of the immune response, and control of host recognition and reaction via the cellular immune system.

The discovery of activation of the class Ia antigens by ocular inflammation is of particular importance in the study of corneal transplantation[16-18,39] The dependence of host recognition on the presence of underlying inflammation has been acknowledged by most observers, but the possible mechanism wherein donor cells can be caused to "show" their foreign antigen had not been known. Other circumstances may also increase the antigenicity of donor corneas, and these must be elucidated. Short-and long-term control of vascularization should continue to be an attainable goal both in the laboratory and the clinical setting.

Short-term control of vascularization by either laser therapy or use of biochemical mediators such as cortisone-heparin pellets may avoid the initial recognition of the donor material as foreign, particularly if such vascular control reduces concurrent inflammation. Although graft rejection can occur in the absence of neovascularization, it is certainly much more common in those conditions in which the cornea is heavily vascularized, such as chemical injury, herpes simplex, or repeated prior graft failure. Long-term control of vascularization by developing inhibitors to such substances as angiogenin offers hope for permanent control of neovascularization in corneal grafting.

The current experience indicates that cyclosporine, which has its primary effect on the T-lymphocytes and inhibits their attack on foreign tissue, may have great utility in high-risk corneal transplant cases.[40,41] As experience grows using this compound in non-ocular solid organ transplantation as well as in uveitis, indications for its use in corneal transplantation can be further explored. The possibility of using this compound locally around the eye further enhances its potential role for control of destructive immunologic processes.

A related development, which permits increased storage time between donor death and transplantation, is the commercial availability of a media that maintains corneal viability for as long as two weeks.[42] This has increased the amount of donor tissue available for matching of donor to potential recipient. Modification of other storage systems may prove even more useful in extending the length of graft storage.

Balance of Effort Within Subprogram

A. Inflammation and Repair

Since the Plan was published there has been a reordering the research categories that have occupied investigators in this area as evidenced by an overall decrease in the number of grants funded in most parts of the Program Base since FY 1981. For example, in 1981 there were 8 grants funded for analysis of corneal matrix materials (B5). In FY 1984 there were 5 grants in this category. There is currently no activity in exploring the role of vitamin A in the regulation of stromal glycoprotein and proteoglycan synthesis (Bl), nor is there any work on an animal model of peripheral inflammatory keratitis (B4). In total, the 13 grants in the Program Base in this area in FY 1981 were reduced to 7 by FY 1984, nearly a 50% reduction in effort. This change was not the result of the Plan's recommendations, which were to sustain the FY 1981 level of effort through FY 1983, but rather attributable to the workings of the traditional NIH peer review process. Two of the Program Base categories, Dl and D2, had a zero funding rate for new grant applications despite the submission of a total of five applications during FY 1983-1984.

At the same time, there was an increase in support related to one of the two Program Development Priorities identified by the Plan: identifying cells and mediators which cause tissue destruction after injury, infection, and autoimmune disease of the cornea (D2). Three grants were funded in 1981 in this category; 5 were recommended by the Plan, and 7 were funded in 1984. Priority Dl, to compare corticosteroids and progestational steroid effects on tissue destruction and healing, which had no funding in 1981, remained without a funded grant in 1984, despite the Plan's recommendation that 2 such grants be funded. There have been 19 grant applications received in this subprogram area in FY 1983-84, but only 7 of them were funded, a 36% success rate. This rate is considerably lower than the average for NEI grants, and may indicate the need for infusion of new ideas and techniques into this research area.

B. Corneal Transplantation

Only one topic was included in the Program Base. This was the development of functional biopolymers for use in the cornea. While there were 2 funded grants on this subject in FY 1981 and a total of 3 were recommended by the Plan for FY 1983, in 1984 only 1 such grant remained funded. There was a similar attrition of funded projects in the five areas identified as Program Development Priorities. There were 9 grants funded in all 5 areas in 1981; there were only 8 funded in FY 1984 in the face of the Plan's recommendation of 14 by 1983. Activity has attained the Plan's expectation only in the area of the immunology of the allograft reaction (D2), but has fallen short even in the study of tissue compatibility in transplants (Dl). Both exploration of cytotoxic antibodies (D4) and drugs to modify or eliminate allograft reaction (D3) were unfunded in FY 1984, with only one grant application in these two areas combined in FY 1983-84.

A major multicenter study to investigate the role of host-compatibility antigens and tissue typing on the survival of cornea grafts is underway, funded by the National Eye Institute.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

A. Inflammation and Repair

In general, it appears that the Program Base categories delineated in the Plan for the subprogram area were either too detailed and specific, or did not lend themselves to investigation by currently available methods. There appears to be a loss of interest in the whole general topic of corneal matrix synthesis and regulation, as evidenced by the modest number of applications received in this field in FY 1983-84. Of even greater consequence is the relatively poor success rate of applications generally in this subprogram area, reaching only 36%. This suggests that research in this area is slowed by older methods and a lack of creative approaches to the problem. There may also be some lack of enthusiasm for continued work on these problems, since clinically applicable information has been skimpy. For example, the great interest in collagenase and its inhibitors in the 70's has not led to the development of a single clinically useful inhibitor of ulceration, unless medroxyprogresterone proves to fulfill this purpose. In the same way, the lack of conclusive results in the ascorbate-citric acid therapy for chemical injury serves to dampen enthusiasm for continued basic research in the mechanism of stromal repair. There is reason to think, however, that the variation found in refractive surgical procedures will spur renewed interest in studies of collagen synthesis and re-modeling, as well as the turnover of other matrix components.

Certainly there is a recrudescence of interest in the subject of corneal vascularization and its control. It is interesting to note that corneal vascularization was not singled out as a Program Development Priority in the Plan. The central role of vascularization in the evaluation of inflammation, and its importance as a pathologic process in a variety of ocular diseases, warrants its being in the forefront of research related to inflammation and repair.

B. Corneal Transplantation

The Program Base in this area rests solely on the development of functional biopolymers for use in the cornea. A total of 3 grants were recommended in this category for funding by FY 1983. However, the actual number of funded grants declined from 2 in FY 1981 to 1 in FY 1984 despite the receipt of four applications in FY 1984. This suggests that while interest remains in this area, methods and creativity have not been sufficiently worthy to command additional funding.

Because the level of activity recommended in the Plan has been achieved for the investigation of the lymphocytes involved in the allograft reaction and the manipulation of cellular immunological control mechanisms (D2), this activity should now be considered part of the Program Base.

Determining the importance of histocompatibility and tissue-specific antigen (Dl) should remain a Program Development Priority despite the recent funding of a multicenter study on this subject. No further new activity in this area needs funding at this time.

Development and testing of drugs to modify or eliminate the corneal allograft reaction remains a priority. The lack of application of cytotoxic antibody in other systems led the Panel to recommend dropping this recommendation. The post-operative complications of endothelial cell loss, glaucoma, and cystoid macular edema have been adequately studied, but the Panel believes that astigmatism remains the single most important and frequent complication after keratoplasty.

Recommended Changes in Program Base and/or Program Development Priorities

A. Inflammation and Repair

The Panel believes that the Program Base previously identified was too specific, and in some cases rather remotely applicable to understanding disease processes. For these reasons, it recommends combining four of the five categories into the more general category of "determine regulatory mechanisms and therapeutic approaches to corneal stromal ulceration." Two grants are recommended for this area. The Program Development Priority D2 to "identify cells and mediators that cause tissue destruction after injury, infection, and autoimmune diseases of the cornea" has achieved even more activity than the Plan envisioned and can now be continued as a Program Base activity, kept at the currently-funded level of 7 grants.

Significant changes are suggested for the Program Development Priorities in this area. These include a new category: the determination of the regulatory mechanisms involved in the maintenance of normal corneal stroma and stromal wound healing (D1). The potential and need for the development of animal models of peripheral inflammatory keratitis leads the Panel to recommend that this area, previously included in the Program Base, become a Priority (D2).

B. Corneal Transplantation

The Program Base in this area had been limited to the development of functional biopolymers for use in the cornea. In view of the potential importance of these materials, the Panel believes this should remain as the Program Base and at the currently funded level of one grant. The adequacy of support and activity in the Program Development Priority of understanding the allograft reaction and manipulating immunological control mechanisms (D2) makes it possible to move this to the Program Base with continued funding recommended at the current level of 3 grants.

The Program Development Priority concerning histocompatibility and tissue-specific antigens in corneal transplantation (D1) is still of high priority, although recommended additional funding can be somewhat reduced in view of the large multicenter study of this topic now underway. Development of drugs to modify or eliminate the allograft reactions (D3) is still important, and the Panel recommends that 2 grants be funded in this area. The control of corneal astigmatism (included in D5) should remain a priority and should account for 2 funded projects. Evaluation of the role of cytotoxic antibody in corneal graft rejection and the use of blocking and anti-idiotype antibodies to modify allograft reactions (D4) are no longer considered to be useful approaches to the study allograft rejection reactions; therefore, Program Development Priority D4 was eliminated from the subprogram.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL TRANSPLANTATION AND STROMAL WOUND HEALING: INFLAMMATION AND REPAIR (2-J2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Define role of vitamin A in regulation of stromal glycoprotein and proteoglycan synthesis. (B1)	1	1	0	0	0	3	0	
2. Determine limits of ascorbate, cyanoacrylate in treatment of alkali burns and corneal wound repair. (B2)	2	2	2	2	1	2	0	
3. Study enzymology of proteoglycan synthesis and degradation with reference to corneal injury. (B3)	1	1	1	0	1	4	1	25.0
4. Develop animal models of peripheral inflammatory keratitis. (B4)	1	1	0	0	0	0	0	
5. Develop methods for analysis of minute quantities of corneal matrix materials. (B5)	8	8	6	4	5	5	4	80.0
TOTAL FOR PROGRAM BASE	13	13	9 [0]	6 [0]	7 [0]	14	5	35.7
PROGRAM DEVELOPMENT PRIORITIES								
1. Compare corticosteroidal and progestational steroids effect on tissue destruction and wound healing. (D1)	0	2	0	0	0	0	0	
2. Identify cells and mediators which cause tissue destruction after injury, infection, and autoimmune diseases of the cornea. (D2)	3	5	7	7	7	5	2	40.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	3	7	7 [0]	7 [0]	7 [0]	5	2	40.0
TOTAL FOR SUBPROGRAM	16	20	16 [0]	13 [0]	14 [0]	19	7	36.8
(% OF PROGRAM)	(9.8)	(9.3)	(9.8)	(8.6)	(9.2)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL TRANSPLANTATION AND STROMAL WOUND HEALING: INFLAMMATION AND REPAIR (2-J2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Determine the regulatory mechanisms and therapeutic approaches to corneal stromal ulceration. (B1)	LESS SPECIFIC (COMBINES B1, B2, B3, B5)	1	2	0	1	2
2. Identify cells and mediators which cause tissue destruction after injury, infection, and autoimmune diseases of the cornea. (B2)	MOVED (WAS D2)	7	7	0	4 [1]	6
TOTAL FOR PROGRAM BASE		8 [0]	9	0	5 [1]	8 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Determine the regulatory mechanisms involved in the maintenance of normal corneal stroma and in stromal wound healing. (D1)	NEW	6	7	0	7	7
2. Develop animal models of peripheral inflammatory keratitis. (D2)	MOVED (WAS B4)	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		6 [0]	8	0	7 [0]	7 [0]
ADDITIONAL RESEARCH CATEGORIES						
1. Other. (A1)		0	0	0	1	1
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES		0 [0]	0	0	1 [0]	1 [0]
TOTAL FOR SUBPROGRAM		14 [0]	17	0	13 [1]	16 [0]
(% OF PROGRAM)		(9.1)	(7.9)	(0.0)	(7.8)	(9.3)

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL TRANSPLANTATION AND STROMAL WOUND HEALING: CORNEAL TRANSPLANTATION (2-J3)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Develop functional biopolymers for use in the cornea. (B1)	2	3	1	1	1	4	1	25.0
TOTAL FOR PROGRAM BASE	2	3	1 [0]	1 [0]	1 [0]	4	1	25.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Determine importance of histocompatibility and tissue specific antigens in corneal transplantation. (D1)	5	6	6	5	4	3	0	
2. Amplify understanding of allograft reaction by defining types of lymphocytes involved. Investigate potential of manipulating immunological control mechanisms. (D2)	2	3	3	2	3 [1]	5	2	40.0
3. Develop and test drugs which have potential to modify or eliminate allograft reaction. (D3)	1	2	1	0	0	1	0	
4. Evaluate role of cytotoxic antibody in corneal graft rejection and use of blocking and anti-idiotype antibodies to modify allograft reaction. (D4)	1	2	1	1	0	0	0	
5. Determine mechanisms of post-transplant complications. Develop methods to control corneal contour irregularity after anterior segment surgery. (D5)	0	1	0 [1]	0	1	1	1	100.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	9	14	11 [1]	8 [0]	8 [1]	10	3	30.0
TOTAL FOR SUBPROGRAM	11	17	12 [1]	9 [0]	9 [1]	14	4	28.6
(% OF PROGRAM)	(6.8)	(7.9)	(7.4)	(6.0)	(5.9)			

REVISED SUBPROGRAM RESOURCE TABLE

CORNEAL DISEASES

CORNEAL TRANSPLANTATION AND STROMAL WOUND HEALING: CORNEAL TRANSPLANTATION (2-J3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Develop functional biopolymers for use in the cornea. (B1)	SAME	1	1	0	1	1
2. Amplify understanding of allograft reaction by defining types of lymphocytes involved. Investigate potential of manipulating immunological control mechanisms. (B2)	MOVED (WAS D2)	3 [1]	3	0	3	2
TOTAL FOR PROGRAM BASE		4 [1]	4	0	4 [0]	3 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Determine importance of histocompatibility and tissue-specific antigens in corneal transplantation. (D1)	SAME	4	2	9	13	15
2. Develop and test drugs which have potential to modify or eliminate allograft reaction. (D2)	SAME (WAS D3)	0	2	0	0	0
3. Develop methods to control corneal astigmatism after anterior segment surgery. (D3)	SHORTENED (WAS D5)	1	2	0	1 [1]	1 [1]
	[DELETED OLD OLD B1, D4]					
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		5 [0]	6	9	14 [1]	16 [1]
TOTAL FOR SUBPROGRAM		9 [1]	10	9	18 [1]	19 [1]
(% OF PROGRAM)		(5.8)	(4.6)	(45.0)	(10.8)	(11.0)

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CATARACT

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Cataract Panel

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UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

CATARACT

			Figures shown below are Number of Projects [New Mechanisms] (Percent of Projects in Program) Dollars in Thousands			Applications FY 1983-84		
	FY 1981	Panel Rec. FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
1. The Normal Lens (3-D1)	31 (30.7) 3,145	38 (27.7) 4,104	32 [1] (31.4) 3,407	31 [3] (33.0) 3,794	37 [1] (35.9) 4,044	45	25	55.6
2. Epidemiology of Cataract (3-E1)	0 (0.0) 0	7 (5.1) 756	0 [0] (0.0) 0	0 [0] (0.0) 0	1 [0] (1.0) 317	4	1	25.0
3. Senile Cataract (3-F1)	24 (23.8) 2,158	33 (24.1) 3,564	27 [0] (26.5) 2,731	26 [3] (27.7) 2,981	30 [1] (29.1) 3,292	52	25	48.1
4. Diabetic and Metabolic Cataract (3-G1)	19 (18.8) 1,417	23 (16.8) 2,484	17 [2] (16.7) 1,360	12 [0] (12.8) 1,241	14 [0] (13.6) 1,693	28	8	28.6
5. Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses (3-H1)	6 (5.9) 530	11 (8.0) 1,188	6 [0] (5.9) 521	6 [0] (6.4) 586	4 [0] (3.9) 407	4	2	50.0
6. Cataract Induced by Environmental and Toxic Effects (3-J1)	11 (10.9) 986	11 (8.0) 1,188	11 [1] (10.8) 1,040	12 [0] (12.8) 1,328	12 [1] (11.7) 1,261	18	4	22.2
7. Treatment of Cataract and Correction of Aphakia (3-K1)	10 (9.9) 734	14 (10.2) 1,512	9 [2] (8.8) 879	7 [0] (7.4) 672	5 [1] (4.9) 412	10	1	10.0
PROGRAM TOTAL	101 (100.0) 8,970	137 (100.0) 14,796	102 [6] (100.0) 9,938	94 [6] (100.0) 10,602	103 [4] (100.0) 11,426	161	66	41.0

REVISED PROGRAM RESOURCE TABLE

CATARACT

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
		Research Grants	Clinical Trials		
1. The Normal Lens (3-D1)	33 [1] (31.7) 3,560	37 (33.6)	3 (21.4)	34 [1] (32.7) 4,205	39 [2] (35.1) 4,419
2. Epidemiology of Cataract (3-E1)	1 [0] (1.0) 317	3 (2.7)	1 (7.1)	2 [0] (1.9) 741	3 [1] (2.7) 617
3. Senile Cataract (3-F1)	39 [1] (37.5) 4,297	29 (26.4)	5 (35.7)	39 [2] (37.5) 4,619	39 [1] (35.1) 4,454
4. Diabetic and Metabolic Cataract (3-G1)	10 [0] (9.6) 1,359	20 (18.2)	1 (7.1)	11 [1] (10.6) 1,242	7 [1] (6.3) 854
5. Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses (3-H1)	4 [0] (3.8) 407	6 (5.5)	0 (0.0)	3 [0] (2.9) 348	4 [1] (3.6) 402
6. Cataract Induced by Environmental and Toxic Effects (3-J1)	12 [1] (11.5) 1,163	10 (9.1)	2 (14.3)	10 [0] (9.6) 1,126	12 [1] (10.8) 1,340
7. Treatment of Cataract and Correction of Aphakia (3-K1)	5 [1] (4.8) 412	5 (4.5)	2 (14.3)	5 [3] (4.8) 763	7 [1] (6.3) 903
PROGRAM TOTAL	104 [4] (100.0) 11,515	110 (100.0)	14 (100.0)	104 [7] (100.0) 13,044	111 [8] (100.0) 12,989

The Normal Lens

1

Perspective on Recent Research

The Plan's chapter on The Normal Lens covered the following aspects of this transparent ocular tissue: development, structure, epithelial cell growth (in vivo and in vitro), fiber cell differentiation, molecular genetics, physiology and cell communication, physicochemical basis of transparency, and intermediary metabolism (proteins, lipids and carbohydrates). A great deal of work has been published in all these areas since the Plan was written, indicating the current interest and importance of understanding the biological basis for normal lens function. Indeed, only by comparison with the normal, transparent lens will it be possible to understand the nature of cataract.

Two areas that have advanced considerably since publication of the Plan include transport channels in lens cell membranes and molecular biology. The development of small-tipped, calcium-sensitive electrodes, patch clamping, and recombinant DNA techniques are responsible for the current strides in these areas. Molecular genetics in particular has enormous potential for furthering our understanding of the normal and cataractous lens, since experimentation with genes provides new insight into protein structure, regulation, and control of cell behavior.

Progress in Areas Discussed in the 1983-1987 Plan

At the time the Plan was written, crystallin cDNAs were being isolated; crystallin gene isolation was in its infancy. Today, many crystallin cDNAs from many different species have been sequenced (for example[1-7]). In addition, numerous crystallin genes have been cloned and sequenced (see [8] for review). These studies have resulted in a much deeper understanding of these crystallins, their genetic derivations and the basis for their heterogeneity.

Since publication of the Plan, the exon pattern of the β- and γ- crystallin genes has been correlated with the structural motifs of their encoded proteins,[9-12] tremendous progress has been made in characterizing the genomic organization of the β-, γ- and δ-crystallin gene families,[8,10,11,13] and alternative RNA splicing has been established as a mode for producing crystallin heterogenity of primary gene products.[14] Of special importance, crystallin gene isolation has permitted analysis of the sequences that regulate their expression. Microinjection experiments have demonstrated that the δ-crystallin gene has regulatory sequences that direct its tissue-specific expression.[15]

Transfection experiments using fusion genes containing crystallin gene regulatory sequences linked to the bacterial chloramphenicol acetyltransferase gene have identified a few hundred nucleotides at the 5' end of the crystallin genes as the regulatory elements.[16,17] In fact, one such recombinant gene containing the murine α-crystallin gene regulatory sequences has been recently inserted into the germ line of a mouse. This has resulted in a transgenic line that expresses the bacterial enzyme only in the lens and in no other tissue of the organism.[18] These experiments have initiated genetic engineering studies in the lens and clearly have enormous implications. For example, it is now theoretically possible to insert any gene into the chromosomes and to direct its expression specifically in the lens. Genetic experiments of this sort open new opportunities for creating phenotypic changes in lens cells and for overcoming genetic lesions resulting in hereditary diseases, such as the Philly cataract, which may be due to a crystallin gene deficiency.[19] The newly acquired ability to introduce and express foreign genes in cultured lens cells may also have an impact on the study of their growth and differentiation. An example is the introduction of the δ-crystallin gene into the chromosomes of mouse teratocarcinoma stem cells.[20]

Apart from the usefulness of altering the phenotype of lens cells, identification of the regulatory sequences for crystallin genes allows studies on the isolation of lens-specific trans-acting regulatory factors and eventual isolation of the genes regulating the expression of crystallin genes. Thus, we are presently at a crossroads where cloned lens genes can be used both to understand and modify their cellular effects and to unravel the mechanisms responsible for their tissue-specific expression.

Not only crystallin genes have been isolated recently. Numerous other cDNAs end genes of central importance to lens development and function have been cloned and characterized. Notable examples include vimentin[21] and MP26.[22] Vimentin is one of the major cytoskeletal elements of lens cells and MP26 is the gap function protein. Mutagenesis and expression studies allow a powerful new analysis of the structure and function of these and other lens proteins. Such investigations will certainly have a profound effect on our understanding of the normal lens and ultimately on our understanding of cataract.

New and Developing Areas of Research

Two exciting new techniques that have recently become available promise to greatly expand our understanding of lens electrophysiology. It is now possible to construct small-tipped, calcium-sensitive electrodes that are able to measure the activity of free calcium in lens fiber cells.[23,24] Previous techniques for measuring lens calcium determined the total fiber calcium including the bound portion and the extracellular portion; however, it is the free cytoplasmic calcium that is relevant in determining enzyme reaction rates and ion channel gating. Because it is well known that calcium metabolism is often disrupted in cataractous states, this new technique should help determine the specific way in which calcium interacts with cell mechanisms.

The second new technique now being applied to lens membranes is that of the patch voltage clamp.[25-28] In this technique, a small patch of membrane from a lens cell is drawn by suction into the tip of a glass electrode. When successfully implemented, the technique allows one to record the currents that flow through single ionic channels in the membrane patches and to determine the selectivity of the channels, their spatial distribution, and their kinetics of opening and closing. Single lens epithelial cells and small fiber cells may also be voltage clamped by this technique. Thus, the macroscopic conductance properties of entire cells can be studied. The technique has proven useful for measuring the effect of channel blockers on specific lens channels and may in the future characterize drugs that might be useful therapeutically.

Another area which that progressed appreciably within the last few years is lipid metabolism (see reference 29 for review). The presence of the polyunsaturated fatty acid, arachidonic acid (C20:4), has been clearly demonstrated in lenses of several species. Moreover, cultured lenses and lens epithelial cells have been shown to metabolize this fatty acid by the cyclooxygenase pathway to form prostaglandins and by the lipoxygenase pathway to form leukotrienes and hydroxyeicosatetraenoic acids (HETE'S). These compounds are potent regulators of biological activity in a variety of cell types.

Turnover of the membrane phospholipid, phosphatidylinositol, is known to be tightly coupled to the rate of cell division in the lens. The recent demonstration that certain growth factor receptors and oncogene products have phosphatidylinositol kinase activity,[30,31,32] has led to the view that the phosphatidylinositol pathway is part of the signaling mechanism by which such agents regulate cell growth. Further study of the products formed during phosphatidylinositol degradation in the lens, and of the relationships between growth factors and phosphatidylinositol degradation, may lead to a better understanding of the regulation of lens cell division.

Balance of Effort Within Subprogram

A re-analysis by the Panel of the projects funded in the Cataract Program in FY 1984 resulted in the shifting of three grants originally coded in the Normal Lens subprogram to the Senile Cataract subprogram. (See Chapter 3, Section IV.) One additional grant was reassigned to the Cataract Induced by Environmental and Toxic Effects subprogram. The net result was that 33 rather than 37 grants were associated with the Plan's recommendations concerning the normal lens, five less than the 38 recommended by the Plan for FY 1983.

There were 23 projects recommended for the Program Base, but only 13 were funded; on the other hand, there were only 15 projects recommended for the Program Development Priorities and 20 plus one Small Grant were funded. Particularly noticeable was that there was only a single project funded in Program Base category B1 (Study properties of lens proteins, particularly transparency), even though 6 were recommended. By contrast, it was gratifying that there were 6 projects funded in Program Development Priority D1 (Study molecular biology: gene analysis and nucleic acids) and 14 projects funded in Program Development Priority D2 (Study lens transport processes with associated investigations of the structure and function of gap functions and the composition, structure, and function of the cytoskeleton and cell membranes), when only 5 and 10 projects were recommended in these two categories, respectively.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

In general, the Panel believes that the research categories that make up the Program Base and Program Development Priorities in this subprogram continue to be relevant to current research needs and opportunities. However, some reordering and changes in emphasis are warranted now. For example, the very large increase in funding in Program Development Priority D2 that has occurred since 1981, greatly exceeding the Plan's recommended level, suggests that this category no longer need be singled out for special emphasis. Conversely, new research opportunities afforded by molecular biological techniques for the cellular studies specified in Program Base B2 mandate the reclassification of the category as a Program Development Priority.

Recommended Changes in Program Base and/or Program Development Priorities

Consequently, the Panel suggests that Program Development Priority D2 be moved into the Program Base and somewhat decreased from its FY 1984 level of 16 projects. On the other hand, the explosive productivity of molecular biology and its associated implications for understanding the lens and modifying its genetic make-up should be developed further and kept as a Program Development Priority (Dl). We recommend that molecular biology remain at a funding level of 7 projects over the next two years. It is likely that even further increases will be recommended in the future. Moreover, the usefulness of molecular biology for the study of cultured lens cells is so great that we recommend that Program Base Category B2 (Study cell division, fiber differentiation, and differential protein synthesis) be modified to include studies on the expression of recombinant genes and alteration of lens phenotype in cultured cells, moved to the Program Development Priority category, and increased to 4 projects.

We do not believe that any of the other categories placed in the Program Base should be deleted or moved. The lower-than-expected number of projects in some categories, such as Bl for example, is due to a combination of limited funds and classification of some projects in other Cataract subprograms. In fact, many studies on lens crystallins that are currently being funded are relevant to this area and thus the apparently small number of projects here is not a reflection of lack of interest by the scientific community.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CATARACT

THE NORMAL LENS (3-D1)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Study properties of lens proteins, particularly transparency. (B1)	5	6	3	1	1	3	1	33.3
2. Study cell division, fiber differentiation, and differential protein synthesis. (B2)	6	6	5	3	4	8	3	37.5
3. Study composition, distribution, and metabolism of lens proteins, carbohydrates, and lipids. (B3)	4	4	3 [1]	3 [1]	1	6	2	33.3
4. Study lens morphology: Preparative methods and quantitative techniques. (B4)	0	1	0	3	4	3	2	66.7
5. Study changes in the lens during aging. (B5)	5	6	5	4	4	1	1	100.0
TOTAL FOR PROGRAM BASE	20	23	16 [1]	14 [1]	14 [0]	21	9	42.9
PROGRAM DEVELOPMENT PRIORITIES								
1. Study molecular biology: Gene analysis and nucleic acids. (D1)	3	5	5	4 [1]	7	6	5	83.3
2. Study lens transport processes: Gap junctions, cytoskeleton, and cell membranes. (D2)	8	10	11	13 [1]	16 [1]	18	11	61.1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	11	15	16 [0]	17 [2]	23 [1]	24	16	66.7
TOTAL FOR SUBPROGRAM	31	38	32 [1]	31 [3]	37 [1]	45	25	55.6
(% OF PROGRAM)	(30.7)	(27.7)	(31.4)	(33.0)	(35.9)			

REVISED SUBPROGRAM RESOURCE TABLE

CATARACT

THE NORMAL LENS (3-D1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Study lens transport processes with associated investigations of the structure and function of gap junctions and the composition, structure, and function of the cytoskeleton and cell membrane. (B1)	MOVED (WAS D2)	14 [1]	13	0	11	16
2. Study properties of lens proteins, particularly transparency. (B2)	SAME (WAS B1)	1	3	0	2	2 [1]
3. Study composition, distribution, and metabolism of lens proteins, carbohydrates, and lipids. (B3)	SAME	1	3	0	4	4
4. Study lens morphology: preparative methods and quantitative techniques. (B4)	SAME	4	3	0	4	4
5. Study changes in the lens during aging. (B5)	SAME	3	4	1	2	2 [1]
TOTAL FOR PROGRAM BASE		23 [1]	26	1	23 [0]	28 [2]
PROGRAM DEVELOPMENT PRIORITIES						
1. Study molecular biology: gene analysis and nucleic acids. (D1)	SAME	6	7	0	5 [1]	4
2. Develop cell culture systems to study lens cell division, differentiation, gene transfer and expression, effects of drugs, and metabolism. (D2)	MORE SPECIFIC (WAS B2)	4	4	2	6	7
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		10 [0]	11	2	11 [1]	11 [0]
TOTAL FOR SUBPROGRAM		33 [1]	37	3	34 [1]	39 [2]
(% OF PROGRAM)		(31.7)	(33.6)	(21.4)	(32.7)	(35.1)

Epidemiology of Cataract

2

Perspective on Recent Research

Cataract surgery has now become the most frequently performed operation in persons over age 60, with more than 1 million cataract operations performed annually.[1] Based on a cost of $2500 for surgery and visual rehabilitation, the economic impact of cataract surgery in the United States can thus be estimated as $2.5 billion per year. The magnitude of the problem threatens to worsen in coming decades as the population ages, because cataract is primarily a disease of the elderly. The increase in the size of the elderly population combined with an increased availability of ophthalmic services, improved technology, widespread availability of financial assistance for medical and hospital care, and changes in the indications for cataract surgery suggest that the number of cataract operations will continue to increase unless means are found to prevent or retard the development of cataracts.

Descriptive, analytic, and experimental epidemiologic studies are essential to accomplishing the major goals of the National Eye Institute's Cataract program; that is, to determine the causes of cataract and control or prevent their development. The discussion of this subject in the Plan remains an excellent overview of the current state of research in the epidemiologic field. It does well in describing currently ongoing activities and identifying major needs and opportunities.

Progress in Areas Discussed in the 1983-1987 Plan

One of the major needs, identified in the Plan, in the field of cataract research has been the development of an objective, standardized, and reproducible classification system for in vivo documentation of the type and severity of cataract. In a recent report on cataract research needs published by Helen Keller International, three general approaches that have been taken to develop such a system were discussed: clinical observation of lens opacities and comparison with a series of standard photographs, photographic or video recording of lens opacities for later analysis, or measurement of laser light scattering within the lens.[2] These approaches are being actively explored by NEI-supported investigators in other subprograms of the Cataract program.

The reproducibility of classification schemes remains a problem. An in vitro classification scheme (that can be adapted to in vivo use) first proposed by Chylack[3] and later adopted by the Cooperative Cataract Research Group (CCRG)[4] has been simplified and has been shown to pass miminum standards of reproducibility when used by novice classifiers.[5] Because experienced classifiers greatly exceeded the minimum reproducibility standards, it is reasonable to expect that training and experience will increase classifier performance using this system.

The decline in intracapsularly extracted lenses and the expense of the CCRG stereoscopic camera equipment have made the validation of in vivo classification, using in vitro classification of extracted lenses as the standard, exceedingly difficult. An inexpensive, portable, classification camera has been developed that nearly equals the quality of the original equipment and should therefore allow researchers to assist in the validation process.[6]

New and Developing Areas of Research

The need continues for identification of the risk factors associated with the development of cataract. Current evidence indicates that senile cataract, for example, may develop as the result of complex interactions of a large number of variables in a tissue in which the cells are not replaced.[7] These variables may include genetic and environmental factors.

One such environmental factor, exposure to the ultraviolet (UV) components of sunlight, has been increasingly implicated in the development of cataract. A cross-sectional study of 105 sites in Nepal showed that sites with an average of 12 hours of sunlight had 3.8 times more cataract than sites with an average of seven hour.[8] Another study found an association between the amount of UV radiation exposure at the site of residence and cortical cataract.[9] Because these data are only suggestive of the role of UV exposure in the development of cataract, further studies that take imto account the individual lifetime exposure to UV radiation are needed.

Balance of Effort Within Subprogram

No extramural projects were funded in this subprogram in FY 1981. Recognizing the need for research in the area, the Plan recommended a total of seven projects for FY 1983. Only one project was funded in FY 1984; however, successes in meeting the Plan's recommendations has been greater than indicated by these figures because of epidemiologic-related projects being conducted in other Cataract subprograms and work underway in the NEI intramural program or being funded by non-NEI sources.

The Plan recommends that two projects be funded in FY 1983 to determine risk factors for cataract (Dl). One such project was funded in FY 1984. An additional collaborative U.S.-Indian study of risk factors for cataract was initiated in 1983 utilizing non-NEI funding sources.

The Plan recommends two projects to validate the classification of type/severity of cataracts (D2). This activity is also cited as a Priority in the Senile Cataract subprogram and one such grant was funded in FY 1983 under that subprogram.

The Plan recommends that one investigator be trained in cataract epidemiology in FY 1983 (D3). A two-year fellow interested in cataract epidemiology was recruited by the NEI's Biometry and Epidemiology Program in FY 1984.

The Plan recommends two projects to measure cataracts and their associated visual impairment in defined populations (D3). No grant applications for such research were received during FY 1983-1984.

The Plan recommends two projects in which epidemiologists collaborate in clinical trials to evaluate cataract treatment and prevention (D4). One such project has been funded in the Treatment of Cataract and Aphakia subprogram.

In summary, five of the seven projects recommended by the Plan for the Epidemiology of Cataract subprogram are ongoing although they have not been classified in this subprogram.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Panel found that Program Development Priorities Dl, D4, and D5, as specified in the Plan, are still appropriate for FY 1986-1987. Priority D2 (Validate reproducible and standardized in vivo classifications of type and severity of cataracts), as an integral component of the CCRG, is included in the Senile Cataract subprogram. The recommendation dealing with the training of investigators (D3) was considered inappropriate for these recommendations, which deal strictly with research.

Recommended Changes in Program Base and/or Program Development Priorities

In view of the above the Panel recommends retention of Priorities Dl (determine cataract risk factors), D4 (measure cataracts and their associated visual impairment in defined populations), and D5 (collaborate in clinical trials of cataract treatment and prevention, different modes of cataract surgery and aphakic correction, proposed medical therapies, prevention of cataracts in diabetes) as Program Development Priorities. However, the CCRG-related Program Base and Program Development Priority categories, Bl (Cooperative Cataract Research Group on classification of cataracts) and D2 (validate classification of type/severity of cataracts), should be deleted because they are also included in the Senile Cataract subprogram. The recommendation to train investigators in cataract epidemiology (D3) should also be deleted.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CATARACT

EPIDEMIOLOGY OF CATARACT (3-E1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Cooperative Cataract Research Group on classification of cataracts. (B1)	0	0	0	0	0	0	0	
TOTAL FOR PROGRAM BASE	0	0	0 [0]	0 [0]	0 [0]	0	0	0.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Determine cataract risk factors. (D1)	0	2	0	0	1	1	1	100.0
2. Validate classification of type/severity of cataracts. (D2)	0	1	0	0	0	1	0	
3. Train investigators in cataract epidemiology. (D3)	0	1	0	0	0	0	0	
4. Measure cataracts and their associated visual impairment in defined populations. (D4)	0	1	0	0	0	2	0	
5. Collaborate in clinical trials of cataract treatment and prevention: Different modes of cataract surgery and aphakic correction, proposed medical therapies, prevention of cataracts in diabetes. (D5)	0	2	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	0	7	0 [0]	0 [0]	1 [0]	4	1	25.0
TOTAL FOR SUBPROGRAM	0	7	0 [0]	0 [0]	1 [0]	4	1	25.0
(% OF PROGRAM)	(0.0)	(5.1)	(0.0)	(0.0)	(1.0)			

REVISED SUBPROGRAM RESOURCE TABLE

CATARACT

EPIDEMIOLOGY OF CATARACT (3-E1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Determine cataract risk factors. (D1)	SAME	1	1	1	2	2
2. Measure cataracts and their associated visual impairment in defined populations. (D2)	SAME (WAS D4)	0	1	0	0	0 [1]
3. Collaborate in clinical trials of cataract treatment and prevention: different modes of cataract surgery and aphakic correction, proposed medical therapies, and prevention of cataracts in diabetes. (D3)	SAME (WAS D5) [DELETED OLD B1,D2,D3]	0	1	0	0	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		1 [0]	3	1	2 [0]	3 [1]
TOTAL FOR SUBPROGRAM		1 [0]	3	1	2 [0]	3 [1]
(% OF PROGRAM)		(1.0)	(2.7)	(7.1)	(1.9)	(2.7)

Senile Cataract

3

Perspective on Recent Research

There have been a number of major changes in this field of research since the Plan was published. First, there has been a precipitous drop in the availability of human cataracts as a result of the large increase in extracapsular lens extractions. This has practically eliminated the supply of fresh intact human cataracts thereby presenting serious problems for conducting certain types of research.

A second change is the significant increase in the number of researchers studying the lens. This has been indicated by an increase in the number of presentations at the Association for Research in Vision and Ophthalmology (ARVO) and the International Congress of Eye Research (ICER) dealing with the lens, and these have been presented primarily by young people associated with large research groups.

Another change that has occurred is a steadily increasing number of drugs on the world market that are claimed by their manufacturers to slow or block the formation of aging-related cataract. Yet there is little or no scientific evidence that these compounds can actually do what is claimed for them.[1]

Dramatic progress has been made in developing nuclear magnetic resonance (NMR) to noninvasively monitoring the earliest changes in lens constituents such as ^{31}P and ^{23}Na. These techniques offer the possibility of detecting changes in lens biology well before the appearance of an opacity.

Advances in molecular biology now make it possible to consider genetic manipulation to alter protein expression and investigate the extent to which such alteration affects transparency. The concept is emerging that oxidative insult is related to the onset of senile cataract by producing loss of membrane integrity, loss of Na^+/K^+ ATPase activity, and, at a later time, formation of protein-membrane linkage and protein aggregates. Recent progress has also led to a better understanding of lipids and their role in normal and cataractous lenses.

Progress in Areas Discussed in the 1983-1987 Plan

There have been significant advances in a number of areas. New techniques have been developed for the microdissection of the lens and for stripping concentric layers of fibers from the tissue. With such techniques, it may be possible to consider age and disease-related changes in more accurate terms.

Using a variety of microdissection techniques, including modified forceps with capped tips, investigators have dissected microsections of predetermined regions of the lens.[2,3] With such techniques, material has become available for microanalyses of the tissue; this opens the possibility of examining material from lenses that are subjected to extracapsular extraction. Examination of lens proteins suggests that a 23K component appears to be preferentially removed from the soluble fraction during cataract development. With increase in opacity, the relative decrease in 23K abundance is more pronounced. Furthermore, general protein profiles from clear and opaque regions are significantly different.

Microtechniques have also been employed in the analysis of lens phospholipids and cholesterol levels. Observations of the rotation of fluorophores in the lens membrane have shown that the lens membrane is very rigid and that the rigidity increases in the nuclear region of the tissue.[4] The rigidity has been explained by the high content of cholesterol in the tissue and the increase in the cholesterol/ phospholipid ratio in the nucleus.[5] Now, using new techniques to remove concentric layers of lens fibers, it has been found that in older human lenses, the phospholipid content remains stable throughout most of the tissue but drops in the nuclear region.[6] In contrast, cholesterol is relatively low in the outer cortex, increases in the deep cortex, and then drops in the nucleus. Thus, the continuous increase in the cholesterol/phospholipid ratio is due to changes in both of these constituents.

Calculation of the surface area of the nuclear fiber cell in the older normal human lens suggests that less than one-third of the membrane is composed of the phospholipid bilayer. Such observations suggest a mosaic of phospholipid and cholesterol or some type of membrane fusion.

The work on oxidative insult to the lens now suggests that this may cause cataract.[7] However, it is becoming apparent that the type of oxidative insult must be defined. In the normal lens, oxidation of methionine or cysteine cannot be detected until approximately the sixth decade or life when it is found in the membrane fraction. In cataract, extensive oxidation of methionine and cysteine has been observed.

The oxidative process appears to be initiated at the membrane level and is apparently caused by external agents such as H_2O_2 and possibly photochemical reaction. A 43,000 dalton component found in the normal lens, which is involved in the formation of protein aggregates associated with cataract development and which has been defined as an extrinsic membrane polypeptide, has been subjected to further investigation.[8] This work now indicates that the 43,000 dalton fraction is a chemically and physically heterogenous population of polypeptides composed of dimers of the monomers of the crystallins. These dimers cannot be reduced to their monomeric units by reduction with DTT or mercaptoethanol. Similar dimers can be produced by photolysis of the crystallins. The work suggests that higher molecular weight non-disulfide-linked crystallin monomers also exist in both aged and cataractous lenses.

In examination of the effect on the lens of H_2O_2, an oxidizing agent found in high levels in the aqueous fluid of some cataract patients, attention has been centered on susceptible membrane components. It was shown that H_2O_2 causes an uncoupling of Na^+ and K^+ transport from ATP hydrolysis.[9] The extent of the effect is dependent on the concentration of ATP and the concentrations of Na^+ and K^+. The H_2O_2 modification changes the ATP interaction at the ATP hydrolysis site from negative to positive kinetic cooperativity and dramatically alters the Na^+ effect on ATP hydrolysis.[10]

Lipid peroxides appear to be formed during retinal degeneration and oxidation of the abundant 22:6 polyunsaturated fatty acid. These peroxides are highly reactive, diffusing through the vitreous and possibly causing posterior subcapsular cataracts.[11] The direct contribution of the lipids of the lens to the cataractous process is not clear. The concentration of polyunsaturated fatty acids is very low.[12] Furthermore, no significant changes in the levels of polyunsaturated fatty acid has been found in cataract. Neither are cholesterol oxidation products found despite the high concentration of cholesterol in the lens.[13]

These observations are in marked contrast to the reported extensive oxidation of protein[7] and may be in part explained by relatively high levels of vitamin E (a naturally-occurring antioxidant) in the tissue.[14] In in vitro experiments, the suggestion has been made that lipid oxidation may lead to cataract formation.[15-16] Oxidative degradation does appear to occur under experimental conditions and can be prevented by addition of vitamin E and other antioxidants.

New and Developing Areas of Research

The ability to study tissues noninvasively is moving ahead rapidly. A most attractive approach includes NMR. A number of reports have already appeared in which NMR was used to determine the abundance of ^{31}P components.[17-20] Although these studies indicate the abundance of the ^{31}P components in the intact lens, they do not demonstrate where in the tissue the ^{31}P constituents are located. However, two advances have made it possible to consider spatial localization of the NMR signal. The introduction of the surface coil and its use in conjunction with Hoult's rotating frame zeumatograph provides opportunity to obtain chemical shift information noninvasively in specific slices of the tissue with knowm spatial coordinates. Investigations have employed this technique to localize ^{31}P metabolites in the bovine eye.[21]

In conjunction with laser-excited dyes, NMR signals can be markedly enhanced, allowing the measurement of groups otherwise hardly detectable. Using such techniques [photochemically induced dynamic nuclear polarization (photo-CIDNP)], the solvent excessibility of γ crystallin has been delineated. The results indicate that His-14 and 113 and Tyr-62 and 165 are sufficiently exposed to elicit photo-CIDNP signals.[22]

Another approach involves the use of NMR imaging. Recently, a report of the proton imaging of the eye and the detection of vitreal liquefication was published.[23] Due to the lower sensitivity of the sodium nucleus (approximately 11-fold less than the proton) and its many fold lower concentration,[23] Na distribution has not been reported. Now with an instrument built at Columbia University,[24] it has now become possible to localize Na spatially in the lens with a resolution of 250 microns.[25] The work indicates a sodium gradient from the posterior to the anterior surface of the tissue and supports the pump leak theory model first proposed by Kinsey[26] and Reddy. The results of these experiments suggest that it is now feasible to consider the development of instruments with strong magnetic fields that will allow the detection in the individual of localized changes in lens Na concentration prior to opacification. Other metabolically important constituents such as ^{31}P may also be observed.

Balance of Effort Within Subprogram

The Panel noted that according to the FY 1981-1984 tracking data, the total number of grants funded in this subprogram increased by 25% during this interval, from 24 to 30. Although this amount of increase is significant, it falls short of the 33 grants recommended by the Plan.

A review of the names of principal investigators and titles of the grants classified in the Senile Cataract subprogram suggested that other NEI-supported investigators working on this problem might be found among those classified in other Cataract subprograms. Indeed, after closely examining the content and aims of the other Cataract grants funded in FY 1984, the Panel recommended that 3 grants from The Normal Lens subprogram, 4 grants from the Diabetic and Metabolic Cataract subprogram, and 2 grants from the Cataract Induced by Environmental and Toxic Effects subprogram—a total of 9—be transferred into the Senile Cataract subprogram.

Although, because of the overlapping and often intertwined multiple interests of these projects it is quite understandable why these grants were initially classified in these other subprograms, the Panel believes that the primary objective and greatest degree of effort in these 9 awards are related to aging-related cataracts. Of course, it could be convincingly argued further that research being pursued in still other Cataract grants has a potential bearing on aging-related cataracts. However, in the Panel's judgment, this re-ordering gives a reasonable accounting of those NEI resources that are primarily devoted and most directly related to the solution of this major worldwide health problem.

With the acceptance of this reclassification by the National Advisory Eye Council and the NEI staff, the Panel then re-analyzed and recoded the total of 39 NEI grants plus 1 Small Grant now included in the Senile Cataract in FY 1984 according to their relationship to the Plan's Program Base and Program Development Priorities. This resulted in increases in two FY 1984 Program Base categories (B3 and B4), a decrease in one category (B2), and no change in the two remaining Program Base categories (Bl and B5). The reclassification also resulted in an increase in Program Development Priority D2 which recommends the development of a long-term culture system for the lens. Three grants were found to be concerned with the use of NMR techniques to study the diseased lens, a category not anticipated by the Plan.

The outcome shows a remarkable agreement between the Plan's recommendations and the actual FY 1984 funding allocation in the Senile Cataract subprogram with two exceptions: the NMR grants mentioned above and one noteworthy Program Base area, B4, which concerns the antioxidant defense mechanisms of the lens. Although the Plan recommended only an increase from two to three grants in this category, ten were funded by FY 1984. This is entirely appropriate given the increasing appreciation by cataract researchers during the past few years of the central role that oxidation plays in cataract formation and the many opportunities for fruitful research in this field.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Panel believes that the original Program Base categories continue to be relevant to current research needs and opportunities. No grants have been funded since FY 1982 in Program Development Priority Dl, which is concerned with the effect of environmental factors. Nor have any applications been received in this area since then. The aim of Program Development Priority D2 has in the Panel's view been fulfilled and therefore this category no longer needs to be singled out for special emphasis, although research should continue in this category. A major gap, given current funding patterns, is the lack of a category for NMR studies and for other noninvasive techniques to study cataract.

Recommended Changes in the Program Base and/or Program Development Priorities

For the reason stated in the previous section, the Panel suggests that Priority D2 be added to the existing Program Base categories and re-worded to emphasize the importance of a long-term culture system. Priority Dl, which is covered by recommendations in both the Cataract Induced by Environmental and Toxic Effects and Diabetic and Metabolic Cataract subprograms, should be deleted.

To replace these two categories, two new Priorities should be added: one calling for the development of NMR techniques to study the diseased lens and another for the development of other non-invasive techniques to study cataract.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CATARACT

SENILE CATARACT (3-F1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Study the natural history of the cataractous process and of risk factors. (B1)	0	1	1	0	0	0	0	
2. Study the plasma membrane of normal and cataractous human lens fiber cells and its interaction with cytoskeletal and soluble lens proteins. (B2)	15	16	16	18 [3]	20 [1]	40	18	45.0
3. Characterize light-scattering entities of the cataractous lens. (B3)	5	7	6	2	2	4	1	25.0
4. Study the antioxidant defense mechanisms of the lens and relevant enzyme kinetics. (B4)	2	3	2	4	6	6	4	66.7
5. Develop a cataract classification. (B5)	1	1	1	1	1	1	1	100.0
TOTAL FOR PROGRAM BASE	23	28	26 [0]	25 [3]	29 [1]	51	24	47.1
PROGRAM DEVELOPMENT PRIORITIES								
1. Study environmental factors such as UV light and nutrients. (D1)	1	3	1	0	0	0	0	
2. Develop a culture system for the human lens. (D2)	0	2	0	1	1	1	1	100.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	5	1 [0]	1 [0]	1 [0]	1	1	100.0
TOTAL FOR SUBPROGRAM	24	33	27 [0]	26 [3]	30 [1]	52	25	48.1
(% OF PROGRAM)	(23.8)	(24.0)	(26.5)	(27.6)	(29.1)			

REVISED SUBPROGRAM RESOURCE TABLE

CATARACT

SENILE CATARACT (3-F1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Study the natural history of the cataractous process and of cataract risk factors. (B1)	SAME	0	1	0	0	0
2. Study the plasma membrane of normal and cataractous human lens fiber cells and its interaction with cytoskeletal and soluble lens proteins. (B2)	SAME	16 [1]	16	2	17	17 [1]
3. Characterize the light-scattering entities of the cataractous lens: conduct biochemical studies of high molecular weight protein aggregates and normal proteins and oxidative and other changes that occur with aging. (B3)	SAME	7	3	0	7	7
4. Study the antioxidant defense mechanisms of the lens and relevant enzyme kinetics. (B4)	SAME	10	5	2	9 [2]	9
5. Develop a cataract classification [CCRG]. (B5)	SAME	1	0	1	1	1
6. Develop a long-term culture system for the lens. (B6)	MORE SPECIFIC (WAS D2)	2	1	0	2	2
TOTAL FOR PROGRAM BASE		36 [1]	26	5	36 [2]	36 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop NMR techniques to study the diseased lens. (D1)	NEW	3	2	0	3	3
2. Develop other non-invasive techniques to study cataract. (D2)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	[DELETED OLD D1]	3 [0]	3	0	3 [0]	3 [0]
TOTAL FOR SUBPROGRAM		39 [1]	29	5	39 [2]	39 [1]
(% OF PROGRAM)		(37.5)	(26.3)	(35.7)	(37.5)	(35.1)

Diabetic and Metabolic Cataract

4

Perspective on Recent Research

Increased extracapsular lens extractions have significantly decreased the availability of fresh, intact human cataractous lenses, thereby presenting a serious problem for the biochemical study of diabetic and other metabolic cataracts. This increases the importance of the development of new, noninvasive spectroscopic methods for the study of lens metabolism. Nuclear magnetic resonance (NMR) appears to be one such promising technique, which permits the monitoring of levels of selected metabolic intermediates over time through the use of appropriate probes. Ongoing and projected clinical trials of aldose reductase inhibitors may provide impetus for the rapid development of such techniques so that the efficacy of these agents in altering the metabolism of the lens, as well as other ocular tissues, can be quantitatively assessed on diabetic populations.

Progress in Areas Discussed in the 1983-1987 Plan

Numerous studies provide evidence for the role of aldose reductase and the polyol pathway in the development of diabetic cataracts. Increased levels of polyol pathway intermediates in extracted lenses have been correlated with increased levels of glycosylated hemoglobin (HbAlc) and fasting blood sugar levels.[1] Aldose reductase activity has also been reported to increase in hypermature and senile diabetic cataracts while the levels of glucose-6-phosphate dehydrogenase activity decrease.[2] Moreover, examination of sodium levels in lenses extracted from diabetics and nondiabetics indicate that osmotic stresses induced in the lenses of diabetic and non-diabetic patients are different.[3]

New photographic methods have also been applied to the clinical study of diabetic lenses. Photofluorometry studies indicate that decreases in lens transmission of blue-green light (λ = 490 and 530 nm) as a function of age occur about 15 years earlier in patients with diabetes of more than 10 years duration than in healthy controls.[4] Scheimpflug photography has also been employed in attempts to monitor the progress of diabetic cataracts through linear densitometric evaluation of Scheimpflug photographs.[5]

Studies of the role of aldose reductase and the polyol pathway in diabetic and galactosemic animals has also progressed. Several new aldose reductase inhibitors, including tolrestat (Ayerst) and statil (ICI), and 1-[(p-bromophenyl)-sulfonyl] hydantoins have been reported to inhibit cataract formation in animals.[6-8] NMR has also been successfully employed to monitor the ability of the aldose reductase inhibitor sorbinil (Pfizer) to inhibit aldose reductase-induced metabolic changes in rabbit lenses under in vitro hyperglycemic conditions.[9] Further studies on the ability of sorbinil to reverse the onset of diabetic cataract formation have also been reported.[10-11] These suggest the importance of both the amount of osmotic stress and the administration of inhibitor at levels adequate to counter this stress in the reversal process. The levels of aldose reductase in the galactose-fed rat lens has also been monitored with immunohistochemical staining. These results indicate that staining increases with the onset of cataract, suggesting that the level of aldose reductase increases and that either the administration of sorbinil or removal of galactose diet results in decreased staining for aldose reductase.[12]

Several clinical studies concerning metabolic cataracts have also emerged. Evaluation of erythrocyte galactokinase activity in patients admitted for elective cataract surgery suggests that diminished galactokinase activity may increase the risk of developing presenile cataracts requiring surgery by the fourth decade.[13] The incidence of glucose-6-phosphate dehydrogenase deficiency and the lowered ability of the lenses of these patients to maintain reduced-GSSG has also been reported as risk factors for cataract formation.[14-15] Congenital cataracts have also been observed in a family with sorbitol dehydrogenase deficiency.[16]

New and Developing Areas of Research

Recent advances in molecular genetics may provide tools for the study of metabolic cataracts. Experimental manipulation of genes in either lens cell cultures or animals may result in the development of new and specific models that will aid in understanding clinically observed metabolic cataracts. Such animals models would also stimulate the development of medical treatments for cataracts.

Balance of Effort Within Subprogram

As noted in the discussion of the balance of effort in the Senile Cataract subprogram, four grants paid in FY 1984 that were originally classified in Diabetic and Metabolic Cataract were, upon the Panel's recommendation, transferred to Senile Cataract. Thus, there were 10, rather than 14, grants funded in FY 1984 for research on Diabetic and Metabolic Cataract.

The revised tracking data indicates that the Plan's recommendations for Program Base categories BI, B2, and B3 were essentially fulfilled by FY 1984. Although the number of NEI research grants in category B4 decreased from 4 to 0 since the Plan was published, the evaluation of the safety and efficacy of drugs that may delay diabetic cataract formation is actually an extremely active area of research within the pharmaceutical industry, both in this country and abroad. In fact, two major pharmaceutical companies are engaged in a full-scale research attack on the development of anticataract agents. Therefore, in this instance, the falloff of NEI support for grants in this field may be considered a positive development, because it indicates the readiness of this long-developing area of research for clinical application. It is appropriate that the private sector is now taking up this challenge.

For similar reasons, the falloff in support for category B5 since the Plan was published is due to the fact that the research objective it specifies has been achieved.

The re-analysis of the FY 1984 grants in this subprogram resulted in no grants associated with the two Program Development Priorities.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

In the Panel's judgment the first four Program Base categories continue to be relevant to current research needs and opportunities, whereas, as noted above, category B5 has been accomplished.

The re-analysis of FY 1984 grants in this subprogram drew attention to problems with the wording of the two Program Development Priorities. In the case of DI, as worded, this Priority would seem more appropriately included in the Nongenetic Congenital and Genetic Cataracts and Dislocated Lens subprogram, In the case of D2, there is some overlap with the Epidemiology of Cataract subprogram. In view of recent developments in the field of molecular biology, there is need for a new emphasis on the application of techniques from this field to the study of metabolic cataracts.

Recommended Changes in the Program Base and/or Program Development Priorities

For the reason noted above, the Panel recommends deletion of Program Base category B5. Program Development Priorities DI and D2 should be retained but slightly reworded to make them more sharply focused on the objectives of this subprogram. Finally, a new Program Development Priority should be added (D3) to encourage the use of molecular biologic approaches to research on metabolic cataracts.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CATARACT

DIABETIC AND METABOLIC CATARACT (3-G1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Study the chemical pathways in diabetic and metabolic cataracts. (B1)	3	3	3 [1]	4	7	16	3	18.8
2. Study the metabolism of proteins, especially crystallins, during the formation of diabetic and metabolic cataracts. (B2)	3	3	2 [1]	3	3	5	3	60.0
3. Examine the characteristics of aldose reductase in animal and human lens; drug susceptibility; AR inhibitors. (B3)	4	4	3	4	2	2	1	50.0
4. Determine the safety and efficacy of drugs that may delay diabetic cataract formation. (B4)	4	4	4	0	0	1	0	
5. Establish role of aldose reductase, hexokinase, and sorbitol dehydrogenase in human diabetic cataract formation. (B5)	4	5	4	0	0	0	0	
TOTAL FOR PROGRAM BASE	18	19	16 [2]	11 [0]	12 [0]	24	7	29.2
PROGRAM DEVELOPMENT PRIORITIES								
1. Establish cell lines from animal and human sources with known genetic abnormalities. (D1)	0	2	0	0	1	3	1	33.3
2. Conduct epidemiologic and biochemical studies to establish role of nutrition in cataract formation. (D2)	1	2	1	1	1	1	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	4	1 [0]	1 [0]	2 [0]	4	1	25.0
TOTAL FOR SUBPROGRAM	19	23	17 [2]	12 [0]	14 [0]	28	8	28.6
(% OF PROGRAM)	(18.8)	(16.7)	(16.7)	(12.8)	(13.6)			

REVISED SUBPROGRAM RESOURCE TABLE

CATARACT

DIABETIC AND METABOLIC CATARACT (3-G1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Study the chemical pathways in diabetic and metabolic cataracts. (B1)	SAME	3	8	1	2 [1]	2
2. Study the metabolism of proteins, especially crystallins, during the formation of diabetic and metabolic cataracts. (B2)	SAME	4	3	0	4	1
3. Examine the characterstics of aldose reductase, drug susceptibility, and AR inhibitors in animal and human lenses. (B3)	SAME	3	2	0	4	3
4. Determine the safety and efficacy of drugs that may delay diabetic cataract formation. (B4)	SAME [DELETED OLD D5]	0	1	0	1	1
TOTAL FOR PROGRAM BASE		10 [0]	14	1	11 [1]	7 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Establish cell lines from animal and human sources to study metabolic cataracts. (D1)	MORE SPECIFIC	0	2	0	0	0
2. Conduct biochemical studies to establish the role of nutrition in cataract formation. (D2)	SHORTENED	0	2	0	0	0
3. Apply molecular biology techniques to study metabolic cataracts. (D3)	NEW	0	2	0	0	0 [1]
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	6	0	0 [0]	0 [1]
TOTAL FOR SUBPROGRAM		10 [0]	20	1	11 [1]	7 [1]
(% OF PROGRAM)		(9.6)	(18.1)	(7.1)	(10.6)	(6.3)

Nongenetic Congenital and Genetic Cataracts and Dislocated Lenses

5

Perspective on Recent Research and Progress in Areas Discussed in the 1983-1987 Plan

In the Plan, various key metabolic and genetic diseases connected with cataract were tabulated, some of the better-studied animal models for hereditary cataracts were discussed (especially Nakano mouse and Philly mouse) and current knowledge of the morphology and biochemistry of zonular fibers were reviewed. Unfortunately, there has been relatively little progress in this area since publication of the Plan.

New and Developing Areas of Research

As with studies of the normal lens, recent advances in molecular genetics provide a special opportunity to deepen our understanding of hereditary cataracts to the gene level. The use of cloned cDNA probes has recently demonstrated that the hereditary Fraser mouse cataract is associated with the selective loss of the entire class of γ-crystallin mRNAs.[1] This is due to preferential deterioration of the lens fiber cells during progression of the cataract, and illustrates that recombinant DNA probes can be used to investigate cytoplasmic and pathogenic events as well as gene phenomena per se. It appears as if the time is ripe for further analysis of genetic cataracts and of the zonular fibers with respect to the composition of mRNAs and expression of specific genes.

Balance of Effort within Subprogram

It is interesting that, although there were only 4 funded projects in the subprogram in 1984, 3 of them were in category D3 of the Program Development Priorities (Prepare molecular genetic probes to study the lesions involved in cataracts).

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Program Base and Program Development Priorities categories are all still relevant to current research needs and opportunities; however, the fact that not a single grant application was received in five of the six Priority categories suggests that some of them might be eliminated in order to bring the NEI's program priorities more realistically in line with the current potential and interests of investigators in this field.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends that Priority D3 having developed even beyond the Plan's recommended level in FY 1982-83 should now be made part of the Program Base. Because no grant applications were received in categories D2 (Culture epithelial and fiber cells of the lens for long periods of time) and D5 (Conduct animal model studies of lens dislocation) in the Program Development Priorities, the Panel recommends deleting these recommendations. In the case of D2, this recommendation is covered in the Senile Cataract subprogram (B6). In the case of D5, there seems no immediate prospect of fulfilling this recommendation.

The other Program Development Priorities and Program Base categories should be maintained near or slightly above their current, albeit low, levels in view of their importance to this area of investigation. For example, no projects were funded nor were any applications received for Program Development Priority Dl (Conduct longitudinal studies of genetic cataracts in families); nonetheless, such longitudinal studies and genetic pedigrees are essential for further analysis of human hereditary cataracts at the gene level. The recommended funding level for this area is reduced to one grant as a more realistic goal. Similarly, Program Development Priorities D4 (Perfect the techniques of cell culture of ciliary nonpigmented epithelial cells) and D6 (Characterize the zonular fiber biochemically and immunologically) are vital for eventual understanding of lens attachment and function in the eye, and the Panel would like to see research in these areas. Category D6, in particular, should be fulfilled before molecular genetic studies of the major zonular proteins can be initiated.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CATARACT

NONGENETIC CONGENITAL AND GENETIC CATARACTS AND DISLOCATED LENS (3-H1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Determine the role of the zonule in lens-globe growth. (B1)	1	1	1	1	1	1	1	100.0
TOTAL FOR PROGRAM BASE	1	1	1 [0]	1 [0]	1 [0]	1	1	100.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Conduct longitudinal studies of genetic cataracts in families. (D1)	1	2	0	0	0	0	0	
2. Culture epithelial and fiber cells of the lens for long periods of time. (D2)	1	2	1	1	0	0	0	
3. Prepare molecular genetic probes to study the lesions involved in genetic cataracts. (D3)	3	3	4	4	3	3	1	33.3
4. Perfect the techniques of cell culture of ciliary nonpigmented epithelial cells. (D4)	0	1	0	0	0	0	0	
5. Conduct animal model studies of lens dislocation. (D5)	0	1	0	0	0	0	0	
6. Characterize the zonular fiber biochemically and immunologically. (D6)	0	1	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	5	10	5 [0]	5 [0]	3 [0]	3	1	33.3
TOTAL FOR SUBPROGRAM	6	11	6 [0]	6 [0]	4 [0]	4	2	50.0
(% OF PROGRAM)	(5.9)	(8.0)	(5.9)	(6.4)	(3.9)			

REVISED SUBPROGRAM RESOURCE TABLE

CATARACT

NONGENETIC CONGENITAL AND GENETIC CATARACTS AND DISLOCATED LENS (3-H1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Determine the role of the zonule in lens-globe growth. (B1)	SAME	1	1	0	1	1
2. Prepare molecular genetic probes to study the lesions involved in genetic cataracts. (B2)	MOVED (WAS D3)	3	2	0	2	3 [1]
TOTAL FOR PROGRAM BASE		4 [0]	3	0	3 [0]	4 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Conduct longitudinal studies of genetic cataracts in families. (D1)	SAME	0	1	0	0	0
2. Perfect the techniques of cell culture of ciliary nonpigmented epithelial cells. (D2)	SAME (WAS D4)	0	1	0	0	0
3. Characterize the zonular fiber biochemically and immunologically. (D3)	SAME (WAS D6)	0	1	0	0	0
	[DELETED OLD D2, D5]					
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	3	0	0 [0]	0 [0]
TOTAL FOR SUBPROGRAM		4 [0]	6	0	3 [0]	4 [1]
(% OF PROGRAM)		(3.8)	(5.4)	(0.0)	(2.9)	(3.6)

Cataract Induced By Environmental and Toxic Effects

6

Perspective on Recent Research

Within the last few years, a number of studies have been performed to determine the nature of photochemical reactions involved in the cataractous processes in the human lens and the extent of their contribution to the this process.

Progress in Areas Discussed in the 1983-1987 Plan

Isolation and characterization of modified components from human cataractous lenses has led to the identification of oxindoyl alanine, as a possible photooxidative product of lens tryptophan.[1] The age-related formation of 43,000 dalton components and higher molecular weight species in human lenses was found to be due to the polymerization of the monomeric crystallin polypeptides.[2] These polymers appear to be similar to those found in either the direct or sensitized photolysis of lens crystallins.[2-4] In the latter case, endogenous sensitizers such as the glucoside of 3-hydroxykynurenine have been used. In addition to polymerization, the in vitro photolysis of lens proteins leads to the oxidation of a number of amino acids such as methionine, cysteine and histidine,[5] the development of non-tryptophan fluorescence and, in the presence of 3-hydroxykynurenine, increased Ca^{++}-mediated aggregation.[6]

Numerous experiments have been performed on both the direct and sensitized photoxidation of whole lenses,[7-10] demonstrating that photolytic damage can affect numerous areas of the lens. The direct photolysis of rat lenses, using 337.1 nm radiation, causes the photolytic destruction of lens tryptophan with the concomitant formation of products with absorption extending to 350 nm.[7] The sensitized photolysis of the lens with either exogenous or endogenous sensitizers can lead to damage to the cytosol protein, membrane and/or the pump function of the epithelial cell layer. Protein damage can be detected by numerous changes in chemical and physical properties, including photopolymerization of the crystallins.[8] The photooxidation of membranes can lead to lipid oxidation[9] while damage to pump function and choline uptake.[10,11] Many of these effects can be diminished by the addition of antioxidants such as vitamin E. Of course, it is recognized that the lens is exposed to light all through life. The changes observed under experimental conditions occur to some extent in the normal, aging lens but do not appear to lead directly to cataract.

New and Developing Areas of Research

The Panel did not identify any new and developing areas of research in addition to those described in the above section.

Balance of Effort within Subprogram

As with the other subprograms of Cataract, the Panel's re-analysis of tracking data resulted in some shifts in the coding of grants within the Cataract Induced by Environmental and Toxic Effects subprogram. The Plan recommends that 2 projects to examine the mode of action of cataractogenic drugs (Bl) be funded by FY 1983; 3 were actually funded in 1984. Studies of the potentially cataractogenic effects of ionizing, microwave and, ultraviolet radiation (B3) expanded from 4 to 7 projects (rather than the 6 originally identified) plus one Small Grant in FY 1984. In category B2, support declined from FY 1981 to FY 1984 from 5 to 2 grants.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Plan's Program Base categories remain relevant to current research needs and opportunities.

Recommended Changes in Program Base and/or Program Development Priorities

The only change recommended is to add a new Program Base category (B4) to encourage the application of noninvasive techniques to study drug toxicity in vitro and in vivo.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CATARACT

CATARACT INDUCED BY ENVIRONMENTAL AND TOXIC EFFECTS (3-J1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Elucidate the mode of action of potentially cataractogenic drugs. (B1)	2	2	2	3	3	3	1	33.3
2. Develop culture and animal model systems suitable for studying radiation and toxic effects in the lens. (B2)	5	4	3	4	3	3	0	
3. Study the potentially cataractogenic effects of radiation: Ionizing, microwave, ultraviolet. (B3)	4	5	6 [1]	5	6 [1]	12	3	25.0
TOTAL FOR PROGRAM BASE	11	11	11 [1]	12 [0]	12 [1]	18	4	22.2
TOTAL FOR SUBPROGRAM	11	11	11 [1]	12 [0]	12 [1]	18	4	22.2
(% OF PROGRAM)	(10.9)	(8.0)	(10.8)	(12.8)	(11.6)			

REVISED SUBPROGRAM RESOURCE TABLE

CATARACT

CATARACT INDUCED BY ENVIRONMENTAL AND TOXIC EFFECTS (3-J1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Elucidate the mode of action of potentially cataractogenic drugs. (B1)	SAME	3	2	0	3	3 [1]
2. Utilize culture and animal model systems for the study of radiation and toxic effects in the lens. (B2)	SAME	2	3	0	1	1
3. Study the potentially cataractogenic effects of radiation: ionizing, microwave, ultraviolet. (B3)	SAME	7 [1]	4	2	6	8
4. Apply noninvasive techniques to study drug toxicity in vitro and in vivo. (B4)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM BASE		12 [1]	10	2	10 [0]	12 [1]
TOTAL FOR SUBPROGRAM		12 [1]	10	2	10 [0]	12 [1]
(% OF PROGRAM)		(11.5)	(9.1)	(14.3)	(9.6)	(10.8)

Treatment of Cataract and Correction of Aphakia

7

Perspective on Recent Research

Senile cataract now ranks as the world's leading cause of blindness.[1] This stark single statistic implies that the treatment of cataract is not standardized around the world and that the extracapsular technique used with intraocular lens implantation—which enjoys such widespread acceptance by American patients and physicians—is not acceptable to or is not appropriate for other parts of the world.

How is it that a surgically treatable disease is the leading cause of world blindness? In the United States, technological advances in surgery and intraocular and contact lens manufacture have occurred at a dazzling rate. Although most of the research and development in these areas has been funded by the private, industrial sector and performed by practicing ophthalmologists, the National Eye Institute has, whenever possible, encouraged controlled, clinical trials of new therapeutic modalities. Nevertheless, the Program Base for Treatment of Cataract and Correction of Aphakia is narrow and pursues such goals as: improving cataract extraction by preventing surgical complications, studying the mechanics of lens accommodation and lens-induced uveitis, and using controlled clinical trials of various methods of aphakic correction following cataract surgery. Unfortunately, only 5 projects were funded in this subprogram in FY 1984, whereas the Plan recommended that 14 projects be funded.

That the average American patient facing cataract surgery now can expect a 95 to 97 percent chance of fully successful cataract extraction plus intraocular lens implantation suggests that private funding of further technological research and development is appropriate; it is also appropriate to consider extending the comparatively limited resources of the NEI to solving problems of treating cataract in developing countries. It will be essential to focus world attention on the rapidly escalating problem of cataract-induced blindness if funds and other resources are to be applied effectively to this problem. The NEI, in conjunction with other national and international organizations, will be in a powerful position to focus world attention on and apply effective solutions to their important public health problems.

Progress in Areas Discussed in the 1983-1987 Plan

Nonsurgical Treatment of Cataract. Although no medical treatment of cataract has yet been proved effective, there remains great interest in the group of drugs known as aldose reductase inhibitors. Trials of sorbinil as a treatment for diabetic neuropathy and retinopathy have begun, and a trial of this drug as an anticataract agent is ready to start.

Considerable progress has been made in the development of sensitive, objective methods for measuring cataractous growth in vivo. These methods involve the application of specialized photographic techniques of Scheimpflug slit photography for nuclear cataracts, Neitz retroillumination photography for cortical cataracts and conventional color slit photography for nuclear color documentation.[2,3,4] These films are then subjected to computerized image analysis, a technique that measures cataract size and density. Because these images are standardizable, it is possible to use them for longitudinal (temporal) studies. The variances of these techniques have been measured, and it is now possible to calculate the size of a population needed to test the efficacy of an anticataract drug.

Another promising technique for measuring cataractous change is quasielastic light scattering (QELS); this can measure total light scattered as well as the light scattered from large molecular aggregates and smaller monomeric proteins.[5] QELS may be very useful in field studies of precataractous changes as well as in the testing of anticataract medications.

Correction of Aphakia

Eyeglasses. Aphakic lenses which eliminate wavelengths less than 400 nm have been developed to reduce the likelihood of UV-light damage to the retina.[6] Special lenses have also been introduced to eliminate glare that plagues patients with immature cataracts.

Contact Lenses. As the risks and complications of continuous wear, soft aphakic contact lenses have been publicized and as the success of intraocular lens implantation has increased, the use of these contact lenses has decreased.[7,8]

Intraocular Lenses. During the past three years, the use of posterior chamber lenses has increased tremendously; anterior chamber IOLs are used correspondingly less frequently and iris-clip and iridocapsular lenses are now used rarely.[9]

Posterior chamber implants have been placed in the ciliary sulcus with great success, but recently "in the bag" placements (in which the implant resides entirely within the lens capsule) have gained increasing popularity with no increased risk.

The ability to extract the lens through a small incision in the eye has encouraged the development of foldable silicone implants that can be inserted as a "taco" or through a large-bore needle-like inserter.[10] It remains to be proven that these new soft implants are optically as successful and as safe as their polymethylmethacrylate predecessors.

Most recently intracapsular phacoemulsification has been promoted as a way of removing opacified cortex and nucleus without seriously disrupting the capsular bag.[11] The bag is then filled with a polymer that serves as a new lens. This technically difficult operation remains to be tested and proven as safe and effective as more traditional techniques.

The only NEI funded program assessing the management of cataract in humans is a prospective trial in England assessing the efficacy and safety of treating patients with: 1) intracapsular cataract extraction and contact lenses, 2) intracapsular extraction with iris clip intraocular lens implantation, or 3) extracapsular extraction and iridocapsular lens implantation.[12] It is unfortunate that the results of this study will have little bearing on the course of cataract treatment in this country, since most surgeons here have abandoned all three options in favor of extracapsular extraction with posterior chamber IOL placement.

One of the main nonmechanical complications of intraocular lens implantation is chronic inflammation (uveitis). This may be due to the activation of the complement system which then generates biologically active peptides that can induce tissue injury and inflammation.[13] This research may identify components of the implant, which, if eliminated, could reduce the incidence of this type of inflammation.

Clearly, intraocular lens implantation following extra-capsular extraction will continue to be the treatment of choice for people with serious visual impairment as a result of cataract in the U.S.; it is disconcerting to see the increasing liberalization of the indications for cataract extraction so that in some cases this major surgical procedure is offered to patients with minor, and perhaps trivial, visual complaints. Only through careful clinical research will the true risks/benefits of these procedures be defined so that they will be used only in appropriate circumstances.

Presbyopia. Presbyopia is the gradual age-related loss of focusing power of the eye that results in the need for reading glasses or bifocals in non-myopic individuals. Research supported by the NEI is aimed at understanding and modeling the processes involved in accommodation and studying how these processes change with age and cataract formation.[14] One project studies human accommodation; another, monkey accommodation (30-40 diopters at the age of one year, decreasing to almost zero by age 31 years).[15] The monkey model affords an opportunity to do invasive and noninvasive studies of the processes associated with this age-related loss of accomodative amplitude.

New and Developing Areas of Research

Developing Areas:

Objective Documentation of Cataractous Change In-vivo. The following instruments are commercially available for objectively documenting cataractous change in vivo:

A. Topcon SL-45 (Scheimpflug) slit camera (formerly called the "lens densitograph").

B. Zeiss Video Image Analysis System (does not use film—an updated application of the Scheimpflug principle).

C. Neitz CTR Retroillumination camera.

D. Sasaki's combination retroillumination/Scheimpflug System.

E. Conventional Photoslit and Retroillumination Photography.

F. Quasi-elastic light scattering (Reichert Scientifics' "Ocular Scattering Analyzer" and Kowa's QELS instrument).

It is important to compare and contrast these instruments and select those that are best suited to longitudinal documentation of cataractous change. How these instruments would be used both in the clinic and in the field for a study of the natural or drug-impaired growth of cataracts should be established.

Anti-cataract Drug Trials. The NEI might collaborate with interested pharmaceutical companies and the World Health Organization (WHO) in the development and implementation of clinical protocols for measuring the efficacy of potential anticataract drugs.

The NEI should continue to emphasize the importance of developing improved techniques of cataract management and treatment in infants and children and the influence of aphakia on development of vision in this age group.

New Areas: In June 1986, the NEI in collaboration with Helen Keller International (HKI) and the International Association for the Prevention of Blindness (IAPB) hosted a meeting at the NEI of internationally renowned physicians and scientists involved in care or study of patients with cataract to:

A. Focus attention on the fact that cataract is the world's leading cause of blindness.

B. Define for all the members of the meeting the magnitude of the cataract problem in several regions of the world including (Latin America, India, Africa, and China).

C. Inform the public that currently available methods and resources are not keeping up with the increasing incidence and prevalence of cataract-related blindness.

D. Apply methods of epidemiology and operations research to the problem of cataract-related blindness to discover more efficient and less costly methods of reducing the large and increasing backlog of unoperated cataracts around the world.

In many parts of the third world, intracapsular cataract extraction without intraocular lens insertion is done in an eye camp or rural hospital. Patients are kept at rest in-hospital for 5 to 10 days. By improving the suturing techniques, thereby increasing the likelihood of a water-tight wound closure, it may be possible to discharge patients sooner and get a larger number of patients treated in each hospital facility. There are several other areas in which minor changes in approach may effect large changes in productivity. In a country like India in which there are 1.5 x 10^6 new cataract-blind patients/year and only 1.0 x 10^6 cataract extractions possible/year, such an increase in productivity would benefit large numbers of patients.

The report of their meeting, which recommends several new projects and programs to reduce the worldwide burden of cataract blindness, was published in November 1986.[16]

Balance of Effort Within Subprogram

In the Plan, a total of 14 projects were recommended for this subprogram for FY 1983; 8 of these were in the Program Base and 6 were Program Development Priorities. By FY 1984, there were only five actual projects funded; all but one were in the Program Base. In FY 1984, there were no funded projects in the category "Improve cataract extraction by preventing complications from surgery" (Bl); 3 grants for studies of lens accommodation (B2), and 1 grant each in the study of lens-induced uveitis and the use of controlled clinical trials of various methods of aphakic correction following cataract extraction (B3 and B4).

The studies that were funded offer excellent opportunities to expand our understanding of some of the basic mechanisms of lens accommodation and of the manner in which lens-induced inflammation develops. That the NIH has not funded any studies in the field of cataract extraction might be cause for concern; but in spite of this, in 1984-85 there have been more than 800 articles published in the medical literature dealing with cataract extraction. Clearly, there is support coming from industry, private foundations, and individuals to sustain this remarkable output.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The items listed in the Program Base and the Program Development Priorities apparently did not stimulate a great deal of interest among those in the research community to apply to the NEI for support for research in these targeted areas. It seems that, for whatever reasons, other sources of funding were judged by a very active clinical research community to be preferable to NEI funding. This lack of NEI funding has not slowed research in this area, although it is clear from the magnitude of the problem of unoperated cataract in the third world that this active clinical research community is either not addressing those problems which might reduce this backlog or not addressing them with sufficient vigor or organization.

The NEI, Helen Keller International (HKI), and the International Association for the Prevention of Blindness (IAPB) have together begun to focus world attention on the magnitude of the problem of unoperated cataract in the Third World. Through their efforts, it is clear that the increases in cost of the technologically elegant and highly successful techniques of cataract extraction now used in developed countries are not sufficiently offset by increases in effectiveness to be used by Third World surgeons in their attempt to reduce the backlog of unoperated cataracts. In these settings, it is likely that the Graefe-knife section, enzymatic zonulysis, intracapsular lens insertion, and careful suturing will continue to be the technique of choice.

To reduce the backlog of unoperated cataracts will require careful research into patients' attitudes toward their illnesses, methods of improving access to regional medical facilities, methods of decreasing the length of in-hospital care postoperatively and methods of increasing the numbers and training of medical and paramedical personnel devoted to the care of patients with cataract. Indeed, the opportunities in this branch of world health are many and the likelihood of making a major impact are excellent in view of the many opportunities to achieve large effects with small changes.

Regarding cataract treatment in the United States, it is not as clear what role the NEI can best play at this time. On the one hand there is the real possibility that NEI funding will support research into some treatment modality that is outmoded before the results of the research are in; on the other hand, as in the PERK (radial keratotomy) study, certainly there will be opportunities for peer-reviewed research to present clear unbiased evidence on the efficacy of a controversial new treatment. It may be necessary from time to time to convene a group of clinical researchers to advise the NEI on potentially fruitful initiatives in the field of cataract treatment as practiced in the U.S.

A few years ago the NIH made an estimate that if a medical means of delaying cataract maturation ten years could be found, it would reduce the number of cataract extractions needed by 46 percent. Of course, this estimate counts on the medical treatment being acceptable for the ten-year period as well as the longevity of the population not increasing at all. Although the most efficient long-term solution to the problem of increasing cataract-related blindness throughout the world may be a preventive medication, the immediate need is to maximize the efficiency of existing surgical procedures and delivery systems.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel suggests no changes at this time, other than deleting Priority DI, for which NEI support seems not to be required.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

CATARACT

TREATMENT OF CATARACT AND CORRECTION OF APHAKIA (3-K1)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Improve cataract extraction by preventing complications from surgery. (B1)	0	1	0 [1]	0	0	2	0	
2. Study mechanics of lens accommodation. (B2)	4	2	4	4	3	0	0	
3. Study the mechanisms of lens-induced uveitis. (B3)	1	1	0 [1]	1	1 [1]	1	1	100.0
4. Use controlled clinical trials of various methods of aphakic correction following cataract surgery. (B4)	4	4	2	2	1	0	0	
TOTAL FOR PROGRAM BASE	9	8	6 [2]	7 [0]	5 [1]	3	1	33.3
PROGRAM DEVELOPMENT PRIORITIES								
1. Compare results of various methods of cataract surgery. (D1)	1	3	1	0	0	2	0	
2. Develop improved techniques of cataract management and treatment in infants and children, and the influence of aphakia on development of vision in this age group. (D2)	0	2	1	0	0	4	0	
3. Develop and assess techniques and methods in cataract prevention and treatment. (D3)	0	1	1	0	0	1	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	6	3 [0]	0 [0]	0 [0]	7	0	0.0
TOTAL FOR SUBPROGRAM	10	14	9 [2]	7 [0]	5 [1]	10	1	10.0
(% OF PROGRAM)	(9.9)	(10.2)	(8.8)	(7.4)	(4.9)			

REVISED SUBPROGRAM RESOURCE TABLE

CATARACT

TREATMENT OF CATARACT AND CORRECTION OF APHAKIA (3-K1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Improve cataract extraction by preventing complications from surgery. (B1)	SAME	0	1	0	0 [2]	2 [1]
2. Study mechanics of lens accommodation. (B2)	SAME	3	2	0	3	3
3. Study the mechanisms of lens-induced uveitis. (B3)	SAME	1 [1]	1	0	0	0
4. Use controlled clinical trials of various methods of aphakic correction following cataract surgery. (B4)	SAME	1	0	1	1 [1]	1
TOTAL FOR PROGRAM BASE		5 [1]	4	1	4 [3]	6 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop improved techniques of cataract management and treatment in infants and children, and determine the influence of aphakia on development of vision in this age group. (D1)	SAME (WAS D2)	0	0	1	1	1
2. Develop and assess techniques and methods in cataract prevention and treatment. (D2)	SAME (WAS D3)	0	1	0	0	0
	[DELETED OLD D1]					
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	1	1	1 [0]	1 [0]
TOTAL FOR SUBPROGRAM		5 [1]	5	2	5 [3]	7 [1]
(% OF PROGRAM)		(4.8)	(4.5)	(14.3)	(4.8)	(6.3)

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GLAUCOMA

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Glaucoma Panel

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UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

GLAUCOMA

			Figures shown below are Number of Projects [New Mechanisms] (Percent of Projects in Program) Dollars in Thousands			Applications FY 1983-84		
	FY 1981	Panel Rec. FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
Primary Open-Angle Glaucoma (4-M1)								
1. Etiology, Epidemiology, Management, and Therapy (4-N1)	7 (7.8) 723	16 (12.8) 1,508	8 [0] (9.1) 707	16 [1] (16.3) 1,419	14 [0] (14.4) 1,471	29	10	34.5
2. Aqueous Humor Dynamics: Inflow (4-P1)	27 (30.0) 2,885	34 (27.2) 3,944	29 [3] (33.0) 3,293	31 [1] (31.6) 3,876	35 [1] (36.1) 4,614	37	18	48.6
3. Aqueous Humor Dynamics: Outflow (4-Q1)	24 (26.7) 2,273	28 (22.4) 3,596	23 [1] (26.1) 2,611	21 [1] (21.4) 2,506	18 [0] (18.6) 2,698	25	9	36.0
4. The Optic Nerve (4-R1)	16 (17.8) 1,771	22 (17.6) 2,552	17 [0] (19.3) 1,988	17 [2] (17.3) 2,292	16 [1] (16.5) 2,486	21	8	38.1
Other Glaucomas								
5. Angle-Closure Glaucoma (4-S1)	3 (3.3) 155	6 (4.8) 696	3 [0] (3.4) 180	3 [0] (3.1) 165	2 [0] (2.1) 37	3	2	66.6
6. Developmental, Congenital, and Infantile Glaucomas (4-T1)	2 (2.2) 137	5 (4.0) 580	1 [0] (1.1) 38	1 [0] (1.0) 46	1 [0] (1.0) 53	1	0	0.0
7. Secondary Glaucomas (4-V1)	11 (12.2) 836	14 (11.2) 1,624	7 [0] (8.0) 842	9 [0] (9.2) 1,002	11 [1] (11.3) 1,357	14	6	42.9
PROGRAM TOTAL	90 (100.0) 8,780	125 (100.0) 14,500	88 [4] (100.0) 9,659	98 [5] (100.0) 11,306	97 [3] (100.0) 12,716	130	53	40.8

REVISED PROGRAM RESOURCE TABLE

GLAUCOMA

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
Primary Open-Angle Glaucoma (4-M1)					
1. Etiology, Epidemiology, Management, and Therapy (4-M1)	15 [0] (15.5) 1,684	21 (16.3)	31 (100.0)	24 [0] (24.5) 2,513	18 [4] (18.2) 2,367
2. Aqueous Humor Dynamics: Inflow (4-P1)	36 [1] (37.1) 4,626	29 (22.5)	0 (0.0)	31 [0] (31.6) 4,708	33 [1] (33.3) 4,994
3. Aqueous Humor Dynamics: Outflow (4-Q1)	19 [0] (19.6) 2,876	25 (19.4)	0 (0.0)	20 [0] (20.4) 3,087	20 [0] (20.2) 2,996
4. The Optic Nerve (4-R1)	13 [1] (13.4) 2,085	26 (20.2)	0 (0.0)	12 [2] (12.2) 2,019	16 [2] (16.2) 2,444
Other Glaucomas					
5. Angle-Closure Glaucoma (4-S1)	2 [0] (2.1) 37	5 (3.9)	0 (0.0)	1 [0] (1.0) 18	2 [0] (2.0) 36
6. Developmental, Congenital, and Infantile Glaucomas (4-T1)	1 [0] (1.0) 53	7 (5.4)	0 (0.0)	1 [0] (1.0) 59	0 [0] (.0) 0
7. Secondary Glaucomas (4-V1)	11 [1] (11.3) 1,357	16 (12.4)	0 (0.0)	9 [0] (9.2) 1,149	10 [0] (10.1) 1,329
PROGRAM TOTAL	97 [3] (100.0) 12,718	129 (100.0)	31 (100.0)	98 [2] (100.0) 13,553	99 [7] (100.0) 14,166

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PRIMARY OPEN-ANGLE GLAUCOMA

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Etiology, Epidemiology, Management, and Therapy

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Perspective on Recent Research

Since publication of the Plan, a considerable amount of new basic research has begun, utilizing especially tissue culture and molecular biologic methods to clarify further the physiology and pathology of trabecular meshwork cells in health and disease. These studies, including detailed analysis of tissue biochemistry, should lay a good foundation for improving our understanding of open-angle glaucoma.

In the past three years, major advances have occurred in understanding the distribution of glaucoma and its sequelae in the population. Blacks, myopes, and other groups have been shown, in hospital- and clinic-based studies, to be at increased risk to glaucoma. These have led to the initiation of expanded, definitive population-based and case-control studies. The clarification of risk factors in glaucoma may eventually provide predictive information to aid the identification of patients at risk for development of visual field loss from glaucoma.

Similarly, more refined understanding of patient compliance with prescribed treatment regimens and factors associated with it have led to the initiation of further trials in the search for effective, more acceptable methods of prophylaxis and treatment, including new laser techniques and drugs with fewer side effects.

In particular, laser trabeculoplasty has been widely applied clinically and has been validated as a safe and effective means of providing improved intraocular pressure control for several years following the procedure. Quantitative perimetry has continued to evolve and has clearly provided a marked improvement in our ability to identify and monitor the progression of visual field changes in glaucoma patients. 5-fluorouracil has been used to modify wound healing following glaucoma filtration surgery and appears to have significant promise in improving surgical results, especially in high-risk glaucoma patients. The general topic of wound healing control is under active investigation in multiple centers and holds great promise for improvement of surgical results in glaucoma therapy.

Progress in Areas Discussed in the 1983-1987 Plan

Epidemiologic studies are under way to elucidate risk factors for open-angle glaucoma, especially to evaluate possible racial differences.[1] In population studies, blood pressure and body weight have been found to be positively correlated with intraocular pressure.[2] Myopia has been suggested as a risk factor for open-angle glaucoma.[3,4] Epidemiologic evidence also suggests that migraine is a risk factor for low-tension glaucoma.[5,6]

Three clinical studies are evaluating aspects of medical therapy for glaucoma. A self-tonometer has been developed for home monitoring of intraocular pressure.[7] Preliminary studies indicate that some patients who seem to be losing vision from glaucoma with apparently normal levels of intraocular pressure have, in fact, sporadic elevations of pressure that are not being detected during office visits. A special eyedrop dispenser, that externally resembles an ordinary bottle but internally contains a computer that records times of eyedrop administration, is being used to monitor patient compliance with medical treatment of glaucoma.[8] Initial studies indicate that few patients comply well with instructions for the use of pilocarpine. Nasolacrimal occlusion or even simple eyelid closure has been shown to enhance absorption of topically applied medications into the eye and to reduce their systemic absorption, thus enhancing therapeutic efficacy and reducing the likelihood of adverse systemic side effects.[9]

Two therapeutic randomized clinical trials are under way. In one, postoperative subconjunctival administration of 5-fluorouracil, an antimetabolite that inhibits cell proliferation and enhances the success of filtration surgery in high risk patients, is defining the safety and efficacy of this treatment.[10,11] Numerous studies have documented the efficacy, relative safety, and potential risks of argon laser trabeculoplasty.[12-16] The Glaucoma Laser Trial is comparing the efficacy of argon laser trabeculoplasty with that of traditional medical treatment for newly diagnosed primary open-angle glaucoma.

Unfortunately, we still do not have sufficient understanding of low-tension glaucoma to begin large scale clinical trials. On the other hand, well known and accepted approaches to treating classical open-angle glaucoma have never been subjected to clinical trials capable of defining the value and limitations of lowering intraocular pressure in preventing progressive optic nerve damage. A controlled trial of prophylactic reduction of intraocular pressure in patients at high risk of optic nerve damage (e.g., those with ocular hypertension) would throw important light on this area as well as determine the potential efficacy of present treatment modalities for glaucomatous nerve damage.

New and Developing Areas of Research

Focused transconjunctival ultrasonic energy has been reported to reduce the intraocular pressure in animals and humans.[17] The mechanism of this procedure is unclear and its indications, safety, and long-term efficacy remain to be established.

The success of 5-fluorouracil in enhancing efficacy of filtering surgery in some high risk eyes should encourage the exploration of other potential modifiers of surgical success.

The mechanism by which laser trabeculoplasty increases outflow of aqueous humor remains unexplained, although several theoretical explanations have been proposed. Laboratory research may also define the tissue reactions to the laser treatment as well as provide clues about the mechanism of the outflow obstruction in primary open-angle glaucoma.

The elucidation of risk factors for glaucoma and the loss of vision in glaucoma by modern epidemiologic methods will improve the clinician's prognostic ability, shed light on disease mechanisms, and, perhaps, point the way to new treatments. Many potential risk factors published by the Glaucoma Panel in 1983 are currently undergoing intense epidemiologic investigation; others, such as myopia and migraine, need confirmation.

Finally, there are three areas of great need that await new insights or new methods of approach to stimulate further progress. The first is to devise a noninvasive method to continuously monitor intraocular pressure. The second is to determine if it is possible to identify genetic probes as markers for primary open-angle glaucoma. The third is identification of a natural animal model of primary open-angle glaucoma to facilitate research. Current animal models are useful for the study of aspects of the mechanism of optic nerve damage, but are not useful for the study of aqueous outflow in glaucoma because all have different mechanisms of outflow damage that are different from human eyes with glaucoma.

Balance of Effort Within Subprogram

The Plan recommended continued research activity at the FY 1981 level in all the Program Base categories. This actually occurred through FY 1984 in categories Bl and B2, but the number of projects concerned with clinical studies of drug actions and clinical trials of new drug treatments for primary open angle glaucoma decreased from 4 in FY 1981 to 1 in FY 1984.

Expanded activity is recommended by the Plan in six Program Development Priorities. By FY 1984, the Plan's recommendations were met or exceeded in only two of these: study the epidemiology and natural history of low tension glaucoma (D2) and conduct case control studies of blindness and visual impairment from open-angle and other types of glaucoma (D4). However, in FY 1984 seven grants were awarded for a multicenter clinical trial of laser trabeculoplasty, a project not specifically anticipated by the Plan, but clearly related to the objectives of this subprogram. Thus, overall funding in this subprogram increased from 7 grants in FY 1981 to 14 in FY 1984, only two short of the Plan's FY 1983 projection of 16. Although the expansion envisioned by the Plan in this subprogram did occur in terms of an increased number of grants funded, this growth was not entirely in the areas specifically highlighted by the Plan.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

Most of the Plan's recommendations in this subprogram continue to be relevant, although some of them should be reorganized, recombined, and/or restated in more specific terms. Recommendation Bl concerns aqueous humor outflow and belongs more properly in the Aqueous Humor Dynamics: Outflow subprogram; whereas B2 duplicates an existing recommendation in that subprogram (Dl). Category B3 is much too broad in one sense, combining all clinical studies involving drugs, and too restrictive in another: drugs are the only form of therapy addressed. Clinical trials require more emphasis. Program Development Priority D2 addresses only the epidemiology and natural history of low tension glaucoma; such studies are appropriate for ocular hypertension and open-angle glaucoma as well. Category D6 seems to be much too long-range in outlook and appears to be unnecessary.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends transferring all the Plan's recommendations dealing with clinical research in glaucoma from other subprograms to this subprogram. Conversely, the Panel suggests that recommendations for laboratory research previously included in this subprogram be shifted to the Aqueous Outflow and Optic Nerve subprograms.

The first Program Base category, Bl (Develop and exploit naturally occurring models of impaired aqueous humor outflow), should be moved to the Aqueous Humor Dynamics: Outflow subprogram. Category B2 should be deleted from this subprogram.

Program Base category B3 should be divided into two categories. The first, "Conduct clinical studies on drug actions..." should remain in the Program Base with the addition of "and effects of drug dosages, schedules, and combinations, with emphasis on the effects of chronic administration." The second category, "Conduct clinical trials of new drug treatments for primary open-angle glaucoma," should be expanded to include laser, surgical, and drug treatment and should be placed under Program Development Priorities.

In the Program Development Priorities, Dl should be made more specific by adding that special emphasis should be given to obtaining tissue from untreated cases of open-angle glaucoma for the study of outflow tissues. Category D2 should be expanded to include, in addition to low tension glaucoma, ocular hypertension and primary open-angle glaucoma. Category D3 should be respecified as a clinical trial. Categories D4 and D5 should remain as they are except that in the former, emphasis should be placed on sociologic risk factors and examples of specific risk factors should be noted. With regard to category D6, because there is little likelihood that the goal of a "lasting therapy for primary open-angle glaucoma" will be accomplished in the next decade, it should be deleted as a Program Development Priority.

The Panel also recommends the following additions to the Plan's recommendations. In the Program Base: "Develop improved non-invasive methods for frequent or continuous monitoring of intraocular pressure." In the Program Development Priorities: "Conduct a controlled clinical trial to evaluate treatment of ocular hypertension" and "Conduct studies of physiologic risk factors for optic nerve damage," the latter to be moved from The Optic Nerve subprogram. Furthermore, an "Emerging Areas" category should be added to the Program Development Priorities for classifying such studies as the development of molecular probes for glaucoma.

The transfer of the single grant classified in the original Bl to the Inflow subprogram, and the transfer of two grants from the Optic Nerve subprogram to this subprogram, results in a net gain of one grant for FY 1984, making the total 15 rather than 14.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: ETIOLOGY, EPIDEMIOLOGY, MANAGEMENT, AND THERAPY (4-N1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Develop and exploit naturally occurring models of impaired aqueous humor outflow. (B1)	1	1	1	1	1	3	0	
2. Improve methods for monitoring aqueous humor outflow. (B2)	1	1	1	1 [1]	1	1	1	100.0
3. Conduct clinical studies on drug actions and clinical trials of new drug treatments for primary open-angle glaucoma. (B3)	4	4	3	3	1	2	0	
TOTAL FOR PROGRAM BASE	6	6	5 [0]	5 [1]	3 [0]	6	1	16.7
PROGRAM DEVELOPMENT PRIORITIES								
1. Establish eye donor programs to obtain tissue from glaucoma patients. (D1)	0	1	0	0	0	0	0	
2. Study the epidemiology and natural history of low tension glaucoma. (D2)	0	1	0	0	1	2	1	50.0
3. Evaluate the treatment of low tension glaucoma. (D3)	0	1	0	0	0	0	0	
4. Conduct case-control studies of blindness and visual impairment from open-angle and other types of glaucoma. (D4)	0	1	2	2	2	1	0	
5. Study patient compliance with drug regimens prescribed for treatment of primary open-angle glaucoma. (D5)	1	2	1	1	1	0	0	
6. Pursue research leads toward development of lasting therapy for primary open-angle glaucoma. (D6)	0	1	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	7	3 [0]	3 [0]	4 [0]	3	1	33.3

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: ETIOLOGY, EPIDEMIOLOGY, MANAGEMENT, AND THERAPY (4-H1)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Develop new methods for early diagnosis. (A1)	0	0	0	0	0	1	0	
2. Conduct controlled clinical trials of laser trabeculoplasty. (A2)	0	3	0	8	7	19	8	42.1
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	0	3	0 [0]	8 [0]	7 [0]	20	8	40.0
TOTAL FOR SUBPROGRAM	7	16	8 [0]	16 [1]	14 [0]	29	10	34.5
(% OF PROGRAM)	(7.8)	(12.8)	(9.1)	(16.3)	(14.4)			

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: ETIOLOGY, EPIDEMIOLOGY, MANAGEMENT, AND THERAPY (4-N1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Develop improved non-invasive methods for frequent or continuous monitoring of intraocular pressure. (B1)	NEW	1	1	0	0	1
2. Conduct clinical studies on mechanisms of drug actions and effects of drug dosages, schedules, and combinations, with emphasis on chronic administration. (B2)	MORE SPECIFIC (WAS B3) [B1 MOVED TO 4Q1,D6 DELETED OLD B2]	0	4	0	1	0 [1]
TOTAL FOR PROGRAM BASE		1 [0]	5	0	1 [0]	1 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Establish eye donor programs to obtain and share tissues from well-characterized glaucoma patients, with special emphasis on tissues from untreated cases of open-angle glaucoma. (D1)	MORE SPECIFIC	0	1	0	0	0
2. Study the epidemiology and natural history of low tension glaucoma, ocular hypertension, and primary open-angle glaucoma. (D2)	EXPANDED, MORE SPECIFIC	3	5	0	2	1 [2]
3. Conduct studies of physiologic risk factors for optic nerve damage. (D3)	NEW (MOVED FROM 4R1, D1)	2	4	0	0	0 [1]
4. Conduct studies of sociologic risk factors for blindness and visual impairment from open-angle and other types of glaucoma (e. g., early lack of symptoms, failure to seek medical attention, improper diagnosis and treatment, noncompliance, and failure of therapy). (D4)	MORE SPECIFIC (WAS D4)	0	2	0	1	0
5. Study patient compliance with drug regimens prescribed for treatment of primary open-angle glaucoma. (D5)	SAME	1	2	0	1	0

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: ETIOLOGY, EPIDEMIOLOGY, MANAGEMENT, AND THERAPY (4-N1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
6. Conduct clinical trials of new drug, laser, and surgical treatments for primary open-angle glaucoma. (D6)	MOVED, EXPANDED (WAS B3)	8	0	18	19	16
7. Conduct a controlled clinical trial to evaluate treatment of ocular hypertension. (D7)	NEW	0	0	6	0	0
8. Conduct a controlled clinical trial of the treatment of low-tension glaucoma. (D8)	MORE SPECIFIC (WAS D2, D3)	0	0	7	0	0
9. Other (emerging areas discussed in the text, e. g., molecular probes for glaucoma). (D9)	NEW	0	2	0	0	0
	[DELETED OLD D6]					
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		14 [0]	16	31	23 [0]	17 [3]
TOTAL FOR SUBPROGRAM		15 [0]	21	31	24 [0]	18 [4]
(% OF PROGRAM)		(15.5)	(16.3)	(100.0)	(24.5)	(18.2)

Aqueous Humor Dynamics: Inflow

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Perspective on Recent Research

The Plan cites development of aqueous fluorophotometry and β-adrenergic pharmacology as major areas of research activity over the past few years. The Panel recommends decreased effort in these areas while encouraging additional investigations using the new tools of cell and molecular biology as well as developing data on appropriate models for aqueous humor inflow that are analogous to humans. Although advances to date in aqueous humor inflow have been valuable, the relatively large number of projects in this subprogram should be redistributed somewhat both within the subprogram and among other Glaucoma subprograms.

Progress in Areas Discussed in the 1983-1987 Plan

Understanding of the physiology of aqueous humor formation has benefited greatly from the development of aqueous fluorophotometry. This technique, pioneered many years ago, has in recent years gained widespread interest and acceptance as the method of choice for measuring aqueous humor flow and deducing data on inflow. Several investigators are applying it to studies in the eyes of rabbits, monkeys, and humans.[1-4] There is not yet universal acceptance of specific methods, means for data collection, and of the methods for interpretation of data. Further refinements in these areas will continue to improve the usefulness of fluorophotometry. It has already provided important information about the mechanisms of drug actions, particularly in humans, basic physiological data on the diurnal rhythm of aqueous humor formation, and information on changes in aqueous formation during disease states.[5]

Pharmacologic studies have further refined the specifics of the use of known drugs and introduced potentially useful, new drugs designed to decrease aqueous humor formation. Work with β-adrenergic antagonists has underscored their usefulness,[6-8] and in-depth investigations of dopaminergic compounds have indicated a neural feedback mechanism that may be exploited to regulate inflow and is effective in humans.[9,10] Renewed interest and research in the development of topically effective carbonic anhydrase inhibitors has indicated that this approach may become successful.[11] In addition, earlier studies with cholera toxin[12,13] and the current work with forskolin[14-16] have defined a new class of potentially useful drugs which diminish inflow of aqueous humor; these studies have demonstrated that the intracellular cyclic AMP pathway regulates the formation of aqueous humor and can be meaningfully manipulated. Furthermore, the demonstration that prostaglandins can reduce IOP has raised the possibility that certain of these autacoids may be clinically useful.[17,18]

New and Developing Areas of Research

New areas of physiological research on aqueous humor inflow that should be expanded are the refinement of aqueous fluorophotometry to define uniformly acceptable protocols and interpretations of data, and development of simpler methods. Application of fluorophotometry to measurements of aqueous physiology in primates should further our understanding of mechanisms of drug actions in normal and glaucomatous eyes.

Developing areas in pharmacological research include refinements in the use of adrenergic agents by exploiting new information about beta selectivity, development of carbonic anhydrase inhibitors for topical application, further demonstrations that potent dopaminergic compounds are effective in man, and characterization of the activities of humoral agents, including endogenous peptides, and autacoids that can regulate IOP. Careful investigations of the actions of other agents such as cannabinoid derivatives and direct adenylate cyclase activators should provide useful insights into the mechanisms regulating aqueous humor formation and flow.

Investigations of drug responses should be designed to include observing the changes occurring with chronic administration. Furthermore, it is very important that we begin to acquire systematic information about variations in response to therapy that occur in aged individuals.

Balance of Effort Within Subprogram

This subprogram was judged to be programatically well-balanced; however, a recommendation was made to diminish the level of effort by 10-20%, shifting resources to studies on the optic nerve.

The Plan indicates the need for continued support of basic studies of aqueous humor inflow and increased support for new methods to study fluid movement. It recommends an increase from 27 projects in FY 1981 to 34 in FY 1983 with most of this increase designated for the Program Development Priorities. The projected growth has actually been exceeded in this subprogram; 36 projects were funded in FY 1984, most of the increase has been in the areas identified as Program Development Priorities.

The Panel recommends changing the balance of this subprogram somewhat and diminishing the overall effort by 10%, shifting resources to studies on the optic nerve head. (See Chapter 4.) Contrary to the Plan's recommendations, by FY 1984 there had been a large increase in Program Base projects particularly aimed at pharmacological mechanisms and preclinical new drugs which influence inflow (B2 and B3). The Panel recommends that the total number of projects in the Program Base be reduced from 22 in FY 1984 (of which 18 are related to pharmacology) to 16, with 11 of these in the pharmacological categories B2 and B3. A small increase in funding for cell biology (B5) is recommended.

The Panel recommends a decrease in the number of projects in Program Development Priority Dl as well and encourages investigations that will utilize new methods of molecular biology to study inflow (D3) and those that search for an appropriate model of human aqueous outflow (D4).

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The thrust of the recommendations in the Program Base is judged satisfactory by the Panel. Existing Program Development Priorities need to be more sharply focused by combination or deletion.

Recommended Changes in Program Base and/or Program Development Priorities

No major changes are suggested in the recommendations in the Program Base except to emphasize primate and human studies in Bl and to delete B6 because chemical studies are covered in the Epidemiology, Management Etiology, and Therapy subprogram. As a result of a review of investigators in this area, a grant was reclassified from a miscellaneous category to Bl.

In the Program Development Priorities, the Panel recommends expanding Dl to emphasize fluorophotometry, the major new tool for investigation of aqueous humor formation, and the importance of studies in primates. Priority D3 should be incorporated into Dl, and D4 deleted because its aims are covered within the Etiology, Epidemiology, Management, and Therapy subprogram.

The Panel recommends two new Program Development Priorities. The first (D3) recognizes that expanding information in basic science should now be applied to glaucoma research: Exploit advances in transport physiology, immunocytochemistry, cell biology, and molecular biology to investigate local and intracellular mechanisms that govern aqueous humor formation. The second (D4) emphasizes the need for selection of *appropriate* models for research in aqueous humor production: Determine which subhuman models most closely resemble the human eye for investigation of aqueous humor formation. One FY 1984 grant, previously classified in the Etiology, Epidemiology, Management, and Therapy subprogram was placed in this category, making the total 1984 grants awarded in this subprogram 37 rather than 36.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: AQUEOUS HUMOR DYNAMICS: INFLOW (4-P1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Study the biophysics and biochemistry of fluid exchange, flow, and transport. (B1)	6	5	3	5	3	8	2	25.0
2. Study cellular mechanisms of drug action to alter rate of fluid inflow. (B2)	6	6	10 [2]	10	11	6	3	50.0
3. Conduct studies of the preclinical pharmacology of new drugs that reduce inflow. (B3)	6	5	9	8	7	5	2	40.0
4. Study how inflow processes differ in various types of glaucoma and hypotony. (B4)	1	1	1	1	0	0	0	
5. Study the ultrastructure and cell biology of tissues involved in aqueous humor formation. (B5)	1	1	1	1	1	2	1	50.0
6. Conduct studies to improve present therapeutic measures. (B6)	1	1	0	0 [1]	0	1	1	100.0
TOTAL FOR PROGRAM BASE	21	19	24 [2]	25 [1]	22 [0]	22	9	40.9
PROGRAM DEVELOPMENT PRIORITIES								
1. Apply new methods to studies of the physiology and pharmacology of fluid movement in ciliary body. (D1)	2	6	3	5	8	7	5	71.4
2. Investigate endogenous neural and humoral regulating mechanisms. (D2)	3	4	2 [1]	1	4 [1]	8	4	50.0
3. Develop new noninvasive methods of measuring aqueous humor production. (D3)	0	2	0	0	0	0	0	
4. Develop and test under clinical conditions new medical methods to control aqueous humor production. (D4)	1	3	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	6	15	5 [1]	6 [0]	12 [1]	15	9	60.0
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Other. (A1)	0	0	0	0	1	0	0	
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	0	0	0 [0]	0 [0]	1 [0]	0	0	0.0
TOTAL FOR SUBPROGRAM	27	34	29 [3]	31 [1]	35 [1]	37	18	48.6
(% OF PROGRAM)	(30.0)	(27.2)	(32.9)	(31.6)	(36.1)			

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: AQUEOUS HUMOR DYNAMICS: INFLOW (4-P1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Study the biophysics and biochemistry of fluids exchange, flow, and transport in the eyes of primates and humans. (B1)	MORE SPECIFIC	4	2	0	4	6
2. Study cellular mechanisms of drugs that alter the rate of inflow of aqueous humor. (B2)	SAME	11	6	0	5	5
3. Conduct studies of the preclinical pharmacology of new drugs that reduce aqueous humor inflow. (B3)	SAME	7	5	0	8	9 [1]
4. Study aqueous humor inflow in various types of glaucoma and hypotony. (B4)	SAME	0	1	0	0	0
5. Study the ultrastructure and cell biology of tissues involved in aqueous humor formation. (B5)	SAME [DELETED OLD B6]	1	2	0	1	1
TOTAL FOR PROGRAM BASE		23 [0]	16	0	18 [0]	21 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop new methods, and especially apply fluorophotometry, to studies of the physiology and pharmacology of fluid movement in the eyes of humans and primates. (D1)	MORE SPECIFIC (INCLUDES PREVIOUS D3)	8	6	0	7	3
2. Investigate endogenous neural and humoral regulating mechanisms. (D2)	SAME	4 [1]	4	0	6	8
3. Exploit advances in transport physiology, immunocytochemistry, cell biology, and molecular biology to investigate local and intracellular mechanisms that govern aqueous humor formation. (D3)	NEW	0	2	0	0	1
4. Determine which subhuman models most closely resemble the human eye for investigation of aqueous humor formation. (D4)	NEW [DELETED OLD D4]	1	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		13 [1]	13	0	13 [0]	12 [0]
TOTAL FOR SUBPROGRAM		36 [1]	29	0	31 [0]	33 [1]
(% OF PROGRAM)		(37.1)	(22.5)	(0.0)	(31.6)	(33.3)

Aqueous Humor Dynamics: Outflow

3

Perspective on Recent Research

Advances in cell biology, biochemistry, and morphometric analyses of trabecular meshwork (and other relevant tissues) have aided in the development of recent research on the aqueous outflow pathway. Some of the difficulties in analyzing the small amounts of outflow tissues available for study have been overcome by the application of cell culture methods. These studies have provided interesting new information that will require further verification with physiological and pathological evaluations. Advances have also been made in understanding the possible actions of adrenergic drugs, glucocorticoid hormones, prostaglandins, and other agents which may influence aqueous outflow facility. If cellular studies, in vivo pharmacologic research on the outflow pathway, and evaluations in patients are correlated, these approaches may provide new leads for more effective and more specific methods to lower intraocular pressure.

Progress in Areas Discussed in the 1983-1987 Plan

Research on the aqueous outflow pathway has followed the general themes outlined in the Plan, which emphasized the need to obtain more information concerning the trabecular meshwork and other tissues which may be involved in the regulation of aqueous outflow facility. Biochemical and anatomical methods have been used to examine further the functional properties of the meshwork, including composition and turnover of glycosaminoglycans (GAGs), glycoproteins,[1-10] collagen and other connective tissue elements,[11-16] phagocytosis,[5,17-22] cytoarchitectural elements,[21-24] and the maintenance of an endothelial lining.[5,11] Morphometric evaluations[25] of pathologic specimens have demonstrated that there is damage and loss of trabecular cells that appears to be associated with connective tissue alterations; these changes may result in a loss of normal outflow channels in glaucoma.

This work has pointed to major changes in the corneoscleral meshwork[25-28] and has shifted emphasis somewhat from the prior concentration on the juxtacanalicular tissue as the site of outflow obstruction in primary open-angle glaucoma. Other studies have suggested the possibility that certain glaucoma medications, as well as laser therapy, may cause detrimental changes in the tissues of the outflow pathway,[26-37] emphasizing the need both for further experimental work and for improved treatment protocols.

Pharmacologic studies with adrenergic and cholinergic agents have provided useful information about the specific sites of action of these drugs.[38-43] Some recent studies have provided evidence that subsensitization and drug interactions may influence the effectiveness of therapeutic protocols.[44,45] The use of selective adrenergic agents may provide certain advantages over non-selective agents especially in attempting to preserve the outflow effects of epinephrine when administered with beta-blockers.[46] Experimental manipulation of the anatomy of the outflow pathway using agents such as cytochalasins, EDTA, mercurials, and other agents has been used to gain insight into the mechanisms of the normal resistance to aqueous outflow.[47,48]

The role of prostaglandins in the regulation of intraocular pressure has received new attention following the recent observations that low doses of PGE_2 and $PGF_{2\alpha}$ lower IOP and increase aqueous outflow facility.[49-51] Prostaglandins and other eicosanoids appear to be important autacoids—local regulatory hormones—which can be synthesized in the trabecular meshwork.[52,53] Some drug effects on the meshwork may involve interactions with these substances; for example, in cell culture moderate doses of dexamethasone cause a major decrease in the production of PGE_2 and other prostaglandins.[52,53] Another study has proposed that epinephrine raises the levels of certain prostaglandins and may cause toxicity in primary cultures of trabecular cells.[54]

Glucocorticoid effects on trabecular cells may involve an influence on prostaglandin pathways, but a number of other mechanisms must also be considered. In cultured trabecular cells dexamethasone produces alterations in the accumulation of cell-associated GAGs[8] and in specific protein synthesis.[55,56] The changes in protein synthesis show a time course of induction (1-3 weeks) similar to the time course for the rise in IOP observed with topical administration of dexamethasone in susceptible individuals. It will be of particular interest to examine glucocorticoid effects on cultured trabecular cells from known steroid responders and patients with POAG, if well-defined trabecular cell lines from these patients are obtained. The cell culture studies indicating that there may be a defect in cortisol metabolism in patients with POAG[57,58] did not establish fully that differentiated trabecular cells were obtained, and further research is required to assess these proposals.

Additional interest in the regulation of IOP by glucocorticoids has arisen in part from recent demonstrations that steroids have an acute effect on IOP[59] and by reports that steroid antagonists may lower IOP in rabbits.[60] The latter observation requires further in vivo and in vitro evaluations.

The use of cell culture methods has provided new opportunities to assess the role of trabecular cells in 1) maintaining normal outflow facility, 2) alterations which may take place in different types of glaucoma, and 3) responses to drugs which influence aqueous outflow facility (for example, see reviews[5,21,56]). Trabecular cells from patients of different ages are currently being evaluated in a number of laboratories. However, trabecular meshwork cells from patients with POAG appear to be particularly difficult to propagate, although organ culture studies are possible. The difficulties in obtaining reliable cultures of glaucomatous trabecular cells may involve prior in vivo damage to the cells (which may play a role in the disease process), or these cells may be found to require more exacting culture conditions. Currently, studies of oxidative damage to cultured human trabecular cells[62] are complementing physiologic and biochemical studies of oxidative defense systems of dissected trabecular meshwork tissue.[63,64]

New and Developing Areas of Research

The biological role of the trabecular meshwork in the maintenance of the aqueous outflow facility is under study, focusing upon processes such as phagocytosis, maintenance of endothelial lining, and connective tissue metabolism and cellular cytoarchitecture. New methods are being developed to assess structural and functional changes in the outflow pathway related to glaucoma, aging, and drug therapy.

Investigations are being made of the endogenous regulatory controls of the outflow tissue, including defining the roles of prostaglandins and other potentially important autacoids. Also under study are new drugs and combinations of drugs which influence aqueous outflow facility, e.g., use of selective adrenergic agents, the use of anti-steroids to block glucocorticoid effects, the selection of drugs whose interactions may provide optimal effects or reduced side effects.

Oxidative damage and other mechanisms of injury are being evaluated in relation to the pathologic changes observed in meshwork specimens from aging and glaucomatous eyes. The uses of tissue culture are being further explored as means to assess the role of structural and functional trabecular meshwork cells in normal physiology, with pathological alterations, and following pharmacologic stimulation.

Balance of Effort Within Subprogram

In this subprogram, the Plan's recommendations for the number and distribution of Program Base awards were largely fulfilled. In the Program Development Priorities, the awards made approximated the numbers of projects recommended in Priorities D2 and D4, but no activity occurred in Dl, and the number of grants funded in D3 from 1981 to 1984 slightly increased and then declined below the 1981 level. Nonetheless, the Panel was generally satisfied with the overall balance of awards within and among the Program Base and Program Development sections.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Panel finds that the Program Base and Program Development Priorities in this subprogram continue to be satisfactory, although some sharpening of focus is recommended. New program development priorities are required to capitalize on new opportunities and meet new needs.

Recommended Changes in Program Base and/or Program Development Priorities

Other than sharpening the focus of the Program Base category B2, no changes are recommended in these areas. In the Program Development Priorities the Panel suggests modest expansion of projects in continuing priority areas. It is recommended that Priority D2 be divided into two parts: the first, to remain D2, should emphasize uveoscleral (posterior) outflow and recognize the need for new methods of study; the second part, to be designated as Priority D5 would encourage study of the influence of aqueous humor composition and rate of formation on the outflow pathway. Priority D3 should be reworded to emphasize the development, not just the characterization, of drugs designed specifically to influence target tissues of the outflow apparatus. In Priority D4, the scope of the recommendation should be broadened to allow for factors other than aqueous humor to be considered with respect to failure of filtration surgery.

The Panel also recommends that three new Priorities be added. The first, D6, should incorporate and expand upon the Program Base category Bl, transferred from the Etiology, Epidemiology, Management, and Therapy subprogram, regarding experimental models of outflow obstruction stressing that such models should closely resemble the pathologic and pathophysiologic abnormalities in human primary open-angle glaucoma. Priority D7 stresses the importance of taking advantage of the rapid recent advances in the fields of immunocytochemistry, cell biology, and molecular biology and applying them to investigations of local, hormonal, and cellular mechanisms that influence fluid outflow. The Panel recommends an expansion of awards from 19 to 25 in this area. The final addition, D8, emphasizes the importance of studying changes in the trabecular meshwork following laser treatment for clues to the mechanisms of outflow obstruction in glaucoma and for indications of future complications from this method of therapy.

A re-analysis of the original classification of the FY 1984 Glaucoma grants resulted in the transfer of one grant originally classified as B4 in the Optic Nerve subprogram to this subprogram, making the total funded for FY 1984 in this subprogram 19 rather than 18.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: AQUEOUS HUMOR DYNAMICS: OUTFLOW (4-Q1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Applications FY 1983-84 Funded	Applications FY 1983-84 Percent
PROGRAM BASE								
1. Investigate cell biology of outflow tissues in culture and correlate with in vivo observations in human and primate eyes. (B1)	7	7	7	8	7	8	4	50.0
2. Investigate the morphologic basis of outflow system. (B2)	1	1	1	1	1	1	1	100.0
3. Determine drug effects on the outflow of aqueous humor and intraocular pressure. (B3)	4	4	3	3	2	1	0	
4. Study the biomechanics of normal and abnormal aqueous humor outflow. (B4)	2	2	1	0	1	1	1	100.0
5. Pursue other studies of the normal and abnormal outflow system. (B5)	5	2	5 [1]	3	1	2	0	
TOTAL FOR PROGRAM BASE	19	16	17 [1]	15 [0]	12 [0]	13	6	46.2
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop noninvasive techniques to study normal and abnormal aqueous humor outflow. (D1)	0	2	0	0	0	1	0	
2. Study posterior (uveal) outflow pathways and influence of aqueous humor composition on outflow. (D2)	1	2	0	0	2	2	0	
3. Characterize effects of drugs on target tissues of outflow apparatus and their physiologic correlates. (D3)	4	7	5	5 [1]	3	5	3	60.0
4. Study the basic mechanisms in failure of filtration surgery and the role of aqueous humor factors in wound healing. (D4)	0	1	1	1	1	1	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	5	12	6 [0]	6 [1]	6 [0]	9	3	33.3

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: AQUEOUS HUMOR DYNAMICS: OUTFLOW (4-Q1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Additional Research Categories. (A1)	0	0	0	0	0	3	0	
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	0	0	0 [0]	0 [0]	0 [0]	3	0	0.0
TOTAL FOR SUBPROGRAM	24	28	23 [1]	21 [1]	18 [0]	25	9	36.0
(% OF PROGRAM)	(26.6)	(22.4)	(26.1)	(21.4)	(18.5)			

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: AQUEOUS HUMOR DYNAMICS: OUTFLOW (4-Q1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Investigate cell biology of outflow tissues from normal and diseased eyes in culture and correlate with in vivo observations of human and primate eyes. (B1)	SAME	7	7	0	9	9
2. Investigate the structure of the outflow system in normal and glaucomatous eyes. (B2)	MORE SPECIFIC	1	2	0	1	1
3. Determine drug effects on the outflow of aqueous humor and intraocular pressure. (B3)	SAME	4	4	0	2	1
4. Study the biomechanics of normal and abnormal aqueous humor outflow. (B4)	SAME	1	1	0	2	1
5. Pursue other studies of the normal and abnormal outflow system. (B5)	SAME	1	0	0	0	0
TOTAL FOR PROGRAM BASE		14 [0]	14	0	14 [0]	12 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop noninvasive techniques to study normal and abnormal aqueous humor outflow. (D1)	SAME	1	1	0	0	1
2. Devise methods to study posterior and uveoscleral pathways and their alteration by drugs and disease. (D2)	EXPANDED (FIRST PART OF OLD D2; LATTER PART MOVED TO BECOME D5)	2	2	0	1	2
3. Develop new drugs that influence target tissues of the outflow apparatus to increase aqueous outflow, with special emphasis on blocking or reversing the postulated mechanisms in primary open- angle glaucoma. (D3)	EXPANDED	1	2	0	3	2
4. Study the basic mechanisms involved in failure of filtration surgery. (D4)	BROADENED	1	1	0	0	0

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: AQUEOUS HUMOR DYNAMICS: OUTFLOW (4-Q1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
5. Study the influence of aqueous humor composition and the rate of formation on the outflow pathways. (D5)	MOVED (WAS PART OF OLD D2)	0	1	0	0	0
6. Develop experimental models of outflow obstruction that closely resemble the pathologic and pathophysiologic abnormalities in human primary open- angle glaucoma. (D6)	MODIFICATION OF OLD 4-N1, B1	0	1	0	0	0
7. Take advantage of advances in immunocytochemistry, cell biology, and molecular biology to investigate local and intracellular mechanisms that govern fluid outflow. (D7)	NEW	0	2	0	1	2
8. Evaluate the changes in the trabecular meshwork following laser treatment for clues to the mechanisms of outflow obstruction in glaucoma and for damage that may predict future complications. (D8)	NEW	0	1	0	1	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		5 [0]	11	0	6 [0]	8 [0]
TOTAL FOR SUBPROGRAM		19 [0]	25	0	20 [0]	20 [0]
(% OF PROGRAM)		(19.6)	(19.3)	(0.0)	(20.4)	(20.2)

The Optic Nerve

4

Perspective on Recent Research

Recent advances in the monkey laser-induced glaucoma model, and in human clinicopathologic correlations of glaucomatous optic nerve damage, have enhanced our understanding of the pathogenesis of optic nerve injury in glaucoma. Additional research in these areas should help elucidate the vulnerability of subsets of ganglion cells to glaucomatous damage and provide further details of the mechanism of optic nerve injury.

The early clinical detection and evaluation of glaucoma has been improved by the development of new techniques for imaging and measurement of the optic nerve head, nerve fiber layer photography, automated perimetry, and new clinical methods of psychophysical and electrophysiologic testing. Continuing efforts should be made to refine these procedures for routine clinical use.

Progress in Areas Discussed in the 1983-1987 Plan

Clinicopathologic correlations have disclosed that very significant optic nerve injury precedes and accompanies the initial recognition of field loss in glaucoma.[1] These studies, utilizing light and electron microscopic analyses of human tissues obtained following well-documented clinical disease, emphasize the need to improve methods for detecting early nerve damage and have aided understanding of the mechanisms by which the optic nerve is injured in glaucoma.

Experimental studies continue to confirm the validity of the monkey laser-induced glaucoma model, especially with regard to optic nerve injury in humans.[2,3] This model continues to provide an extremely useful tool for investigation of optic nerve injury in glaucoma, because the anatomy of the disc in the monkey and the pattern of optic nerve injury following pressure insult so closely simulate that in man. Studies of the physiology of the optic vascular system under conditions of elevated intraocular pressure, in the rat and monkey, suggest that the primary pathogenesis of nerve injury in glaucoma is mechanical rather than vascular.[4,5]

Progress has been made toward the development of clinically useful methods for imaging and measuring the optic cup and optic disc surface in glaucoma.[6,8] These continuing studies may lead to an improved ability to correlate clinical findings with visual field results in early glaucoma. The area of the neuroretinal rim has been shown to correlate better with visual field defects in glaucoma than the cop-to-disc ratio.[9]

Nerve fiber layer photography has been improved and demonstrated to represent a clinically useful method of detecting early optic nerve injury in glaucoma which can be correlated with psychophysical testing;[10] it apparently has high sensitivity and specificity in recognizing early visual field loss in glaucoma.[11] Nerve fiber layer photography may be useful as a predictor of which eyes with ocular hypertension are likely to develop visual field defects.

Current research in visual field testing emphasizes the use of automated procedures. Completed clinical evaluations with many automated and semi-automated perimeters[12-14] should aid the practitioner in determining the capabilities, limitations, and proper use of these devices. The development and improvement of automated perimetric test strategies,[15,16] the application of automated perimetry for screening large populations,[16,17] the evolution of quantitative statistical analysis procedures,[15,18-24] and the use of computer simulation to study test strategies, patient response characteristics, and their interactions[25] have all contributed to recent advances in automated perimetry. In particular, the characterization of long- and short-term response fluctuations in normals, ocular hypertensives, and glaucoma patients has aided progress by objectively defining subtle changes in visual field status.[18-24] This area of research is still in its infancy and, with the continuing rapid clinical and commercial expansion of automated perimetry, continuing evaluations of automated visual field testing are needed.

Investigations of acuity perimetry,[26,27] isoluminant chromatic perimetry,[28,29] pattern electroretinograms,[30-32] and other forms of psychophysical and electrophysiologic testing[32-34] have also been conducted within the last few years. Preliminary findings suggest that some of these techniques may be more sensitive than conventional measurement procedures in identifying early glaucomatous visual loss. The clinical efficacy of these new procedures remains to be determined.

New and Developing Areas of Research

Preliminary studies in the monkey model of glaucoma indicate that the magnocellular layers of the lateral geniculate body undergo early atrophy.[35] This finding suggests that selected populations of axons may be especially sensitive to pressure-induced injury. If verified, this study may stimulate the development of improved diagnostic testing and greatly improve the correlation of measurable physiologic changes with early visual field loss in glaucoma. Continuing anatomic and physiologic studies should seek more precise understanding of the vulnerability of subsets of ganglion cells to injury in glaucoma.

Detailed anatomic studies of the retina, nerve fiber layer, and optic nerve head should lead to improved understanding of visual field changes and nerve injury in glaucoma.[36] The exact sequence of anatomical changes underlying clinical visual field changes may be elucidated by quantitative analysis of retinal ganglion cells and axon populations in the monkey laser-induced model for optic nerve injury in glaucoma.

The optic nervehead region should be vigorously explored using new cell biology techniques including micro-histochemistry, enzymology, immunocytochemistry, and tissue culture. The nature of the collagen and other supporting tissues and vasculature, and their respective reactions to increased intraocular pressure in primates and to injury in glaucoma should be explored. Clues may be discovered as to why individual nerves vary in susceptibility to pressure-induced damage. Variations in tissue components (for example; collagen type, isoenzymes, GAG composition) might explain variability in vulnerability to nerve damage in low-tension glaucoma and myopia. Combining quantitative clinical disc measurements and quantitative tissue analyses in the experimental monkey model should permit a precise definition of optic nerve cupping.

The recovery of human autopsy tissues for pathophysiologic correlation should be pursued vigorously through the development of improved donor programs and programs for tissue sharing.

Persistent problems in visual field testing have been associated with distinguishing subtle pathologic changes in visual field status from normal response variations. Research directed towards evaluation of long- and short-term fluctuations in visual field sensitivity, and the development of quantitative statistical analysis procedures[11,14-21] represents the first comprehensive attempt to address these problems. This work should not only be valuable for present purposes, but should also stimulate interest and further research on these issues in the future.

Balance of Effort Within Subprogram

In general, the Panel judged that the balance of effort within this subprogram was acceptable. The Plan emphasized in the Program Base the need for continued support for research pertaining to measurement of optic disc changes, evaluation of mechanisms of glaucomatous optic nerve damage, and development of new psychophysical tests for measuring loss of visual function. In FY 1981, 12 projects were funded in the Program Base. The Plan recommended a redistribution of support between the first 2 categories (decrease "measurement of optic disc changes" by 2 projects and increase "evaluation of mechanisms of glaucomatous optic nerve damage" by 2 projects). However, it was recommended that the total number of projects for the Program Base remain at 12 for FY 1983. In actuality, only eight projects were funded for FY 1984 in the Program Base, with the reductions generally distributed across all of the Program Base categories.

The Program Development Priorities of the Plan emphasized projects related to identifying risk factors for nerve damage, developing noninvasive methods for studying optic nerve damage, developing new psychophysical tests for altered visual function, and evaluating automatic perimetry. In FY 1981, there were 4 projects funded in the Program Development Priorities. The Plan recommended an increase for all categories of the Program Development Priorities to provide a total of 10 projects for FY 1983. There was a total of 7 funded projects for Program Development Priorities in FY 1983, and 8 funded projects in FY 1984 with one Small Business grant funded in each of those years. The Program Development Priority related to development of new psychophysical tests and evaluation of automated perimetry (D3) had only 1 funded project in FY 1983 whereas the Plan had recommended 3. The number of projects in the other Program Development Priorities in FY 1984 were generally in accordance with the Plan's recommendations for FY 1983.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Panel believes that the Program Base and Program Development Priorities needed to be more sharply focused and new Priorities should be added, expanding the subprogram by 10-20 percent.

In particular, with regard to Program Base category Bl, stereophotogrammetry has proven to be only one, and not necessarily the most promising method of documenting structural abnormalities of the neuroretinal rim area and abnormalities of the nerve fiber layers. Other new imaging techniques should all receive added attention.

Program Development Priority Dl continues to be important but is more relevant to the objectives of the subprogram on Etiology, Epidemiology, Management and Therapy. The rapid acceptance of automated perimetry (Priority D3) by the clinical community, a relatively expensive and inadequately tested approach, attests to the need for concrete, effective tests and analytic stragegies for diagnosis and patient management. Promising new work in this area requires further encouragement and resources.

Recommended Changes in Program Base and/or Program Development Priorities

In the Program Base category B1, the phrase "such as stereophotogrammetry" should be deleted to broaden the scope of the category to include other methods such as neuroretinal rim area measurement, pallor measurements, nerve fiber layer dropout, and fluorescein angiography. Category B2 should be broadened to encompass all glaucomatous optic nerve damage. Category B3 is essentially the same as the first part of Program Development Priority D3; therefore, the Panel recommends deleting the current B3 and moving to its place a more detailed statement of the recommendation concerning perimetry, which presently constitutes the second part of D3. A new category, B4, should be added which incorporates the development of psychophysical tests recommended in the first part of D3, emphasizes clinical tests that differ from classic psychophysical methods (B3) and also encourages the interest of electrophysiologists.

This revised Program Base had a total of 8 projects funded in FY 1984. The Panel recommends that the number of funded projects in the Program Base be increased modestly for all categories. These increases would provide a total of 15 projects for the Program Base.

In the Program Development Priorities, the first category, D1, should be deleted from this subprogram and moved to the Etiology, Epidemiology, Management, and Therapy subprogram. Category D2 would then become D1 and should be reworded to emphasize the use of noninvasive methods to study pathophysiologic mechanisms of glaucomatous optic nerve damage in human eyes.

Three new Program Development Priorities, designated D2, D3, and D4, respectively should be added. The first should stress the use of psychophysical and electrophysiological methods to elucidate specific pathologic processes in glaucoma. The second should emphasize histopathologic correlations with clinical measurements of the primate optic nerve head in experimental glaucoma. The third new Priority should encourage the application of new advances in immunocytochemistry and cell biology to study the optic nervehead.

In FY 1984, 5 projects and one Small Business grant fell within the categories of the revised Program Development Priorities. The Panel recommends that the number of projects in the Program Development Priorities be increased to 11.

Overall, there were 13 funded projects (plus one Small Business grant) in FY 1984 that were in accordance with the revised Program Base and Program Development Priorities for the Optic Nerve subprogram. (This reduction from the original 16 resulted from the transfer of two grants associated with the original D1 to the Etiology, Epidemiology, Management, and Therapy subprogram and the shift of the one grant originally classified in B4 to the Outflow subprogram.) The Panel recommends a total of 26 projects for this subprogram to accommodate the growing needs and opportunities in this area which have resulted from recent research advances.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: THE OPTIC NERVE (4-R1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Evaluate methods for measuring and recording changes in the optic disk, such as stereophotogrammetry. (B1)	3	1	3	3	3	0	0	
2. Conduct experimental studies of mechanisms of optic nerve damage in primary open-angle and low tension glaucomas. (B2)	6	8	6	5 [1]	4	4	3	75.0
3. Develop and evaluate new psychophysical tests for measuring optic nerve function and loss of visual function. (B3)	1	1	1	1	0	5	0	
4. Explore other methods for studying optic nerve damage. (B4)	2	2	1	1	1	2	1	50.0
TOTAL FOR PROGRAM BASE	12	12	11 [0]	10 [1]	8 [0]	11	4	36.4
PROGRAM DEVELOPMENT PRIORITIES								
1. Identify risk factors for nerve damage. (D1)	2	3	2	2	2	3	0	
2. Develop new noninvasive methods for studying optic nerve damage and loss of visual function. (D2)	2	4	4	4 [1]	5 [1]	6	3	50.0
3. Develop new psychophysical tests for altered visual function and evaluate automatic perimetry. (D3)	0	3	0	1	1	1	1	100.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	4	10	6 [0]	7 [1]	8 [1]	10	4	40.0
TOTAL FOR SUBPROGRAM	16	22	17 [0]	17 [2]	16 [1]	21	8	38.1
(% OF PROGRAM)	(17.8)	(17.6)	(19.3)	(17.3)	(16.5)			

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

PRIMARY OPEN-ANGLE GLAUCOMA: THE OPTIC NERVE (4-R1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Evaluate methods for measuring and recording changes in the optic disc. (B1)	BROADENED	3	4	0	0	1 [1]
2. Conduct experimental studies of mechanisms of glaucomatous optic nerve damage. (B2)	BROADENED	4	6	0	4	3
3. Develop and validate perimetric methods, including test strategies, analysis procedures, and methods for displaying results. (B3)	NEW (INCLUDES PART OF OLD D3)	1	2	0	2	1
4. Develop clinical psychophysical tests and electrophysiologic methods for measuring altered visual function in glaucoma. (B4)	BROADENED (INCORPORATES OLD B3, D3)	0	3	0	0 [2]	3 [1]
TOTAL FOR PROGRAM BASE		8 [0]	15	0	6 [2]	8 [2]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop new noninvasive methods for studying the pathophysiologic mechanisms of glaucomatous optic nerve damage in human eyes. (D1)	MORE SPECIFIC (WAS D2)	2	5	0	3	5
2. Use psychophysical and electrophysiological methods to elucidate specific pathologic processes in glaucoma, such as types of ganglion cells or axons damaged. (D2)	NEW	3 [1]	2	0	2	2
3. Correlate quantitative clinical descriptions with histopathologic abnormalities produced in the primate optic nerve head by experimental glaucoma. (D3)	NEW	0	2	0	1	0
4. Apply new advances in immunocytochemistry and cell biology to study the optic nerve head as a functional unit of interacting neural, supportive, and vascular tissues in normotensive and glaucomatous eyes. (D4)	NEW [OLD D1 MOVED TO 4N1, D3]	0	2	0	0	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		5 [1]	11	0	6 [0]	8 [0]
TOTAL FOR SUBPROGRAM		13 [1]	26	0	12 [2]	16 [2]
(% OF PROGRAM)		(13.4)	(20.1)	(0.0)	(12.2)	(16.2)

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OTHER GLAUCOMAS

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Angle-Closure Glaucoma

5

Perspective on Recent Research

The principal recent research activities related to angle-closure glaucoma in basic and clinical science have been related to the development of better techniques for laser iridectomy. There is widespread, continuing interest in the YAG laser as possibly the instrument of choice at the present time for this procedure. The precise techniques for both argon and YAG laser iridectomies are continuing to be refined.

A resurgent interest in goniosynechialysis, both by instrumentation and/or visco-surgical methods may lead to modification of techniques for dealing with the sequellae of subacute angle closure.[1]

Progress in Areas Discussed in the 1983-1987 Plan

Laser iridectomy techniques have been demonstrated to be efficient and safe for treatment for angle-closure glaucoma due to pupillary block. This widely-used procedure is undergoing continuing refinement, providing improved results.

Further research is needed to establish the value and reliability of provocative testing in the diagnosis of angle-closure glaucoma in the absence of documented clinical attacks. The indications for iridectomy need to be redefined, given the simplicity and apparent safety of laser iridectomy.

New and Developing Areas of Research

Introduction of the YAG laser and preliminary controlled trials suggest its superiority over the argon laser as a tool for laser iridectomy, because of the ease with which an iridectomy can be made and the reduced tendency to late closure.[2] More extensive, longer-term trials are needed to confirm these advantages and to define indications and risks of YAG iridectomy. It may be, for instance, that the ability of the argon laser to coagulate tissue may make it remain the treatment modality of choice for vascularized irises.

Balance of Effort Within Subprogram

Although the Program Base was maintained at the FY 1981 level through FY 1983 and declined by one grant in FY 1984, no applications were received for grants in either of the two Program Development Priorities.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Plan's overall recommendation for continued development of research in angle-closure glaucoma topics are generally appropriate.

Although few research grants applications are received for studies in this area, the Panel hopes that at least modest progress in funding such projects will be made in subsequent years.

Program Development Priority D2 is obsolete because the use of miotics for the chronic treatment of angle-closure glaucoma is now generally thought to be contraindicated, particularly in view of the efficacy and safety of laser iridectomy.

Recommended Changes in Program Base and/or Program Development Priorities

Program Base Bl should be made slightly more specific by calling for the evaluation as well as the development of predictive tests and diagnostic criteria. The Panel does not recommend any other changes in the Program Base. In the Program Development Priorities, category Dl remains appropriate. Category D2, evaluation of miotic therapy, should be deleted.

Modest expansion of research related to angle-closure glaucoma is recommended. Although angle-closure glaucoma represents a relatively small part of the overall glaucoma research effort, it persists as a major clinical problem and is certainly deserving of continued, vigorous research support. Two projects were actually funded in 1984, and the panel recommends expansion of the subprogram to five projects.

REFERENCES

1. Vela A and Campbell, DG: Modern goniosynechialysis in angle-closure glaucoma. ARVO Abstracts. Invest Ophthalmol Vis Sci 25(Suppl):194, 1984.
2. Robin AL and Pollack IP: A comparison of neodymium: YAG and argon laser iridotomies. Ophthalmology 91:1011, 1984.

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

OTHER GLAUCOMAS: ANGLE-CLOSURE GLAUCOMA (4-S1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Develop predictive and diagnostic criteria for angle closure. (B1)	2	2	2	2	2	2	2	100.0
2. Improve and evaluate therapy for angle-closure. (B2)	1	1	1	1	0	1	0	
TOTAL FOR PROGRAM BASE	3	3	3 [0]	3 [0]	2 [0]	3	2	66.7
PROGRAM DEVELOPMENT PRIORITIES								
1. Describe the pathogenesis of angle-closure glaucoma and subtypes of the disease. (D1)	0	2	0	0	0	0	0	
2. Evaluate the efficacy of initial therapy with miotic drugs in preventing angle-closure in eyes at risk, and determine if any benefit of long-term treatment can be predicted from early drug effects on anterior chamber configuration. (D2)	0	1	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	0	3	0 [0]	0 [0]	0 [0]	0	0	0.0
TOTAL FOR SUBPROGRAM	3	6	3 [0]	3 [0]	2 [0]	3	2	66.7
(% OF PROGRAM)	(3.3)	(4.8)	(3.4)	(3.1)	(2.1)			

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

OTHER GLAUCOMAS: ANGLE-CLOSURE GLAUCOMA (4-S1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Develop and evaluate predictive tests and diagnostic criteria for potential angle-closure glaucoma. (B1)	MORE SPECIFIC	2	2	0	1	2
2. Improve and evaluate therapy for angle-closure glaucoma, and develop or verify tests to identify subtypes of angle-closure glaucoma. (B2)	SAME	0	2	0	0	0
TOTAL FOR PROGRAM BASE		2 [0]	4	0	1 [0]	2 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Describe the pathogenesis of angle-closure glaucoma and subtypes of the disease. (D1)	SAME	0	1	0	0	0
	[DELETED OLD D2]					
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	1	0	0 [0]	0 [0]
TOTAL FOR SUBPROGRAM		2 [0]	5	0	1 [0]	2 [0]
(% OF PROGRAM)		(2.1)	(3.9)	(0.0)	(1.0)	(2.0)

Developmental, Congenital, and Infantile Glaucoma

6

Perspective on Recent Research

Research on glaucoma of infants and children has proven to be an area of great difficulty. Since no adequate animal models exist, the therapeutic demands are great. Some conditions are rare, and few opportunities for clinical research have existed. These problems were reflected in the generality of the Plan's recommendations and by the very small number of projects recommended.

The Panel has broadened the list of Program Development Priorities to stimulate research in directions which are proving valuable in other areas of clinical research, particularly genetics, and population studies, and embryology.

Progress in Areas Discussed in the 1983-1987 Plan

Because of the rare occurrence of this group of diseases and the lack of experimental models, little grant-supported research has been initiated.

One group of investigators, with extensive experience in the treatment of congenital glaucoma, has proposed a new classification, based on clinical appearance of the iris, cornea, and anterior chamber angle.[1] This classification may allow a better definition of prognosis in patients with various clinical types of congenital glaucoma.

New and Developing Areas of Research

No new applicable areas of research have emerged since the publication of the Plan. Ophthalmologists should be urged to investigate advances in developmental anatomy, experimental embryology, and neurobiology for indications of profitable areas of research.

Balance of Effort Within Subprogram

The Plan recommended that three additional awards be made, all in the Program Development category, but no applications were received through FY 1984. There is one ongoing project on classification of these diseases.

This situation is due to the lack of tangible research leads in this difficult field of study. The Panel, realizing this problem, has recommended new ways to approach studies of these types of glaucoma, which seek to generate genetic and experimental development study data.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The Panel determined that the first Program Base category B1, to properly classify these disease entities and perhaps better define their treatment, remains relevant but that the second category, B2—to conduct experimental studies in animals—is too general.

The first Program Development Priority, D1—establishment of a registry for exchange of specimens—remains relevant, but the cooperative program called for in D2 is unlikely to be successful because of the small number of patients available in this country. In other clinically difficult areas, population studies and genetics have provided leads to understanding diseases. Elsewhere in the world, where inbreeding is high, higher prevalences of these diseases may justify research efforts to understand them. Genetic studies may well provide a basis for significant molecular and development research.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends that the Program Base category B1, Classification of childhood glaucoma, remain the same but that B2 be made more specific by limiting it to improving measurement of intraocular pressure in children and making it a Program Development Priority (D3).

With regard to the other Program Development Priorities, the first, to develop a national registry, should remain the same. Priority D2, recommending cooperative studies, should be modified to include the study of populations with a high incidence of congenital glaucoma. Three new Priorities should be designated in addition to D3: D4 to apply molecular genetics to the study of primary congenital glaucoma, D5 to encourage embryologic studies of outflow tissues, and D6 to study the influence of genetic and environmental factors on the etiology of congenital glaucoma.

REFERENCES

1. Hoskins HD, Shaffer RN, and Hetherington J: Anatomical classification of the developmental glaucomas. Arch Ophthalmol 102:1331, 1984.

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

OTHER GLAUCOMAS: DEVELOPMENTAL, CONGENITAL, AND INFANTILE GLAUCOMA (4-T1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Develop a classification system for childhood glaucoma. (B1)	1	1	1	1	1	0	0	
2. Conduct experimental studies in animals. (B2)	1	1	0	0	0	1	0	
TOTAL FOR PROGRAM BASE	2	2	1 [0]	1 [0]	1 [0]	1	0	0.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Establish a national registry of surgical and postmortem specimens from children with developmental, congenital, and infantile glaucoma. (D1)	0	1	0	0	0	0	0	
2. Develop cooperative programs to improve understanding of natural history and treatment of glaucoma in children. (D2)	0	2	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	0	3	0 [0]	0 [0]	0 [0]	0	0	0.0
TOTAL FOR SUBPROGRAM	2	5	1 [0]	1 [0]	1 [0]	1	0	0.0
(% OF PROGRAM)	(2.2)	(4.0)	(1.1)	(1.0)	(1.0)			

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

OTHER GLAUCOMAS: DEVELOPMENTAL, CONGENITAL, AND INFANTILE GLAUCOMA (4-T1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Develop a classification system for childhood glaucoma. (B1)	SAME	1	1	0	1	0
TOTAL FOR PROGRAM BASE		1 [0]	1	0	1 [0]	0 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Establish a national registry for the exchange and study of surgical and postmortem specimens from children with developmental, congenital, and infantile glaucoma. (D1)	SAME	0	1	0	0	0
2. Search for and study populations with high incidence of congenital glaucoma to improve understanding of the natural history of glaucoma and its treatment in children. (D2)	MODIFIED	0	1	0	0	0
3. Improve the means of measuring intraocular pressure and visual function in children. (D3)	MOVED, MORE SPECIFIC (WAS B2)	0	1	0	0	0
4. Apply molecular genetic methods to the study of primary congenital glaucoma. (D4)	NEW	0	1	0	0	0
5. Conduct embryologic studies to elucidate the normal and abnormal development of outflow tissues. (D5)	NEW	0	1	0	0	0
6. Determine the effects of genetic and environmental (maternal and perinatal) factors on the etiolog congenital glaucoma. (D6)	NEW	0	1	0	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	6	0	0 [0]	0 [0]
TOTAL FOR SUBPROGRAM		1 [0]	7	0	1 [0]	0 [0]
(% OF PROGRAM)		(1.0)	(5.4)	(0.0)	(1.0)	(0.0)

Secondary Glaucomas

7

Perspective on Recent Research

Little clinical research has been initiated in these areas, for several reasons: rarity of some of the conditions, lack of new rationales for therapy, and a lack of experimental models for development of fundamental data and clinical paradigms. The major focus of activity has been basic studies of possible mechanisms of anterior inflammation which could relate to the etiology of glaucoma secondary to inflammation. This area of research has benefited greatly from new research opportunities, developed since the Plan was written, in immunology and cell biology that promise to shed light on ocular inflammatory processes.

Progress in Areas Discussed in the 1983-1987 Plan

Goniosynechialysis has been described as an effective surgical treatment to lyse peripheral anterior synechiae and to restore aqueous outflow in synechial angle-closure glaucoma.[1]

A new form of transient secondary glaucoma following YAG laser posterior capsulotomy has been described.[2,3] This seems to be caused by outflow obstruction, the exact mechanism of which remains unclear.[4]

New and Developing Areas of Research

Progress in understanding of secondary glaucomas depends in large part on progress in research on the underlying diseases that cause the glaucoma. Thus, new insights into vasoproliferative processes, inflammatory mediators, and lens protein changes with cataract formation, for example, will in turn lead to better understanding of certain secondary glaucomas.

Balance of Effort Within Subprogram

As noted above, there have been no clinical studies initiated recently, nor have controlled natural history studies been proposed. The Plan's recommendation to reduce support for research into the pathogenetic mechanisms of inflammatory glaucoma has been ignored. The rationale behind the recommendation was that most cases of inflammatory glaucoma occur secondary to posterior uveitis, a condition under active investigation in the Retinal and Choroidal Diseases Program. Given the state of knowledge in the field at the time the Plan was written, it is understandable that those who drafted this section would recommend redirection of support to other areas where more immediate opportunities for productive research existed. However, since the Plan was prepared this entire field has opened up due to the rapid advances in immunology and cell biology that have attracted several investigators to study anterior uveitis and the role of inflammatory mediators in the pathogenesis of inflammatory glaucoma. Thus, support in Program Base category Bl not only did not decrease as projected, but increased from 7 to 9 grants from 1981 to 1984. The Panel believes that support for this area should be maintained, but at a slightly reduced level given the relevance of related work supported in the Retinal and Choroidal Diseases Program, with additional resources slated for other areas of need that are presently not so well-supported. For clinical studies, the relative rarity of some of the secondary glaucomas should justify cooperative study programs. Valid animal models would encourage study of experimental therapeutic measures.

Adequacy and Current Relevance of the Program Base and Program Development Priorities

The first Program Base category, to understand the etiologies of inflammatory glaucomas, remains relevant and is adequately funded; similarly category B2, to understand the low frequency glaucomas, also remains relevant. However, because the natural history of neovascular glaucoma is well-described (Dl), it is no longer necessary for this to be a Program Development Priority. With regard to Priorities D2 and D3, these are areas of ongoing natural history research in which the current level of activity is adequate. Some of this research, particularly that classified in D3, is also covered by the Retinal and Choroidal Diseases Program. For Priorities D4 and D5, there is need to develop new treatments for neovascular and inflammatory glaucomas, not to just test available methods. Research on etiology and treatment of glaucoma secondary to inflammations and on treatment for neovascular glaucoma has been hampered by lack of valid experimental models.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends retaining the first category of the Program Base. The second category B2 should be combined with the Program Development Priority D2 since both are concerned with low frequency glaucomas. Program Development Priorities Dl and

D3 both address aspects of neovascular glaucoma research and should be combined and moved to the Program Base. With regard to Priorities D4 and D5, they should be retained and expanded to emphasize the need to develop new treatments for neovascular and inflammatory glaucoma. A new Priority emphasizing the need fo. development of valid animal models of secondary glaucomas should be added.

REFERENCES

1. Campbell DG and Vela A: Modern goniosynechialysis for the treatment of synechial angle-closure glaucoma. Ophthalmology 91:1052, 1984.
2. Vine AK: Ocular hypertension following Nd:YAG laser capsulotomy: A potentially blinding complication. Ophthalmic Surg 15:283, 1984.
3. Channell MM and Beckman H: Intraocular pressure changes after neodymium-YAG laser posterior capsulotomy. Arch Ophthalmol 102:1024, 1984.
4. Smith CB: Effect of Neodymium: YAG laser posterior capsulotomy on outflow facility. Glaucoma 6:171, 1984.

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

GLAUCOMA

OTHER GLAUCOMAS: SECONDARY GLAUCOMAS (4-VI)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Study the pathogenetic mechanisms of inflammatory glaucoma. (B1)	7	3	4	6	9	7	5	71.4
2. Study the pathogenetic mechanisms of low frequency glaucomas and test therapies. (B2)	1	1	1	1	1	1	0	
TOTAL FOR PROGRAM BASE	8	4	5 [0]	7 [0]	10 [0]	8	5	62.5
PROGRAM DEVELOPMENT PRIORITIES								
1. Study the natural history of neovascular glaucoma. (D1)	1	2	0	0	0	0	0	
2. Study the natural history of low frequency glaucoma. (D2)	1	2	1	1	1	1	0	
3. Study the pathogenetic mechanisms of neovascular glaucoma. (D3)	1	3	1	1	0	2	0	
4. Test treatments for neovascular glaucoma. (D4)	0	1	0	0	0	1	0	
5. Test treatments for inflammatory glaucoma. (D5)	0	2	0	0	0	0	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	3	10	2 [0]	2 [0]	1 [0]	4	0	0.0
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Develop phacolytic glaucoma treatment. (A1)	0	0	0	0	0 [1]	2	1	50.0
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	0	0	0 [0]	0 [0]	0 [1]	2	1	50.0
TOTAL FOR SUBPROGRAM	11	14	7 [0]	9 [0]	11 [1]	14	6	42.9
(% OF PROGRAM)	(12.2)	(11.2)	(7.9)	(9.2)	(11.3)			

REVISED SUBPROGRAM RESOURCE TABLE

GLAUCOMA

OTHER GLAUCOMAS: SECONDARY GLAUCOMAS (4-V1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Study the natural history and pathogenic mechanisms of inflammatory glaucomas. (B1)	SAME	9 [1]	7	0	9	9
2. Study the natural history, pathogenic mechanisms, and therapy of other low frequency glaucomas. (B2)	EXPANDED (COMBINES B2, D2)	1	4	0	0	0
3. Study the natural history and pathogenic mechanisms of neovascular glaucoma. (B3)	MOVED (COMBINES D1, D3)	1	2	0	0	0
TOTAL FOR PROGRAM BASE		11 [1]	13	0	9 [0]	9 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop and evaluate new treatments for neo? vascular glaucoma. (D1)	EXPANDED (WAS D4)	0	1	0	0	0
2. Develop and evaluate new treatments for inflammatory glaucoma. (D2)	EXPANDED (WAS D5)	0	1	0	0	0
3. Develop animal models of common secondary glaucomas that can be used for testing new therapies. (D3)	NEW	0	1	0	0	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		0 [0]	3	0	0 [0]	1 [0]
TOTAL FOR SUBPROGRAM		11 [1]	16	0	9 [0]	10 [0]
(% OF PROGRAM)		(11.3)	(12.4)	(0.0)	(9.2)	(10.1)

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

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Strabismus, Amblyopia, and Visual Processing

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UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

		Panel Rec.	Figures shown below are Number of Projects [New Mechanisms] (Percent of Projects in Program) Dollars in Thousands			Applications FY 1983-84		
	FY 1981	FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
Visual Processing and Amblyopia (5-G1)								
1. **Normal and Abnormal Development (5-G2)**								
a. **Molecular (5-G3)**	19 (7.1) 1,675	25 (7.1) 2,450	13 [1] (5.3) 1,153	14 [1] (5.4) 1,558	18 [0] (6.8) 2,022	36	12	33.3
b. Cell and Systems (5-G4)	51 (19.0) 4,682	44 (12.5) 4,312	45 [1] (18.4) 4,765	51 [0] (19.8) 5,400	46 [1] (17.3) 4,988	64	26	40.6
c. Behavior (5-G5)	12 (4.5) 832	16 (4.5) 1,568	10 [0] (4.1) 700	10 [1] (3.9) 848	7 [1] (2.6) 664	14	7	50.0
SUBPROGRAM TOTAL	82 (30.6) 7,189	85 (24.1) 8,330	68 [2] (27.9) 6,618	75 [2] (29.2) 7,806	71 [2] (26.7) 7,674	114	45	39.5
2. Structure and Function (5-G6)								
a. Molecular (5-G7)	6 (2.2) 579	17 (4.8) 1,666	8 [0] (3.3) 624	9 [0] (3.5) 790	9 [1] (3.4) 913	8	5	62.5
b. Cell and Systems (5-G8)	62 (23.1) 5,212	61 (17.3) 5,978	55 [1] (22.5) 5,207	58 [3] (22.6) 5,981	58 [2] (21.8) 6,691	80	35	43.7
c. Behavior (5-G9)	38 (14.2) 2,779	32 (9.1) 3,136	30 [4] (12.3) 2,167	25 [1] (9.7) 2,191	27 [2] (10.2) 2,494	62	18	29.0
SUBPROGRAM TOTAL	106 (39.6) 8,570	110 ([illegible]) 10,780	93 [5] (38.1) 7,998	92 [4] (35.8) 8,962	94 [5] (35.3) 10,098	150	58	38.7
3. Disorders (5-H1)								
a. Amblyopia (5-H2)	9 (3.4) 646	24 (6.8) 2,352	12 [2] (4.9) 1,143	10 [0] (3.9) 924	16 [1] (6.0) 1,610	46	9	19.6

UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

Figures shown below are Number of Projects [New Mechanisms] (Percent of Projects in Program) Dollars in Thousands

		Panel Rec.				Applications FY 1983-84		
	FY 1981	FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
b. Sensory Neuro-Ophthalmic (5-H3)	1 (0.4) 74	8 (2.3) 784	1 [0] (0.4) 46	1 [0] (0.4) 45	0 [0] (0.0) 0	6	0	0.0
SUBPROGRAM TOTAL	10 (3.7) 720	32 (9.1) 3,136	13 [2] (5.3) 1,189	11 [0] (4.3) 969	16 [1] (6.0) 1,610	52	9	17.3
Ocular Motility and Strabismus (5-J1)								
4. Normal and Abnormal Development (5-J2)	5 (1.9) 439	17 (4.8) 1,666	5 [0] (2.0) 468	5 [0] (1.9) 482	6 [0] (2.3) 569	4	2	50.0
5. Structure and Function (5-J3)								
a. Conjugate Eye Movements (5-J4)	39 (14.6) 3,277	45 (12.7) 4,410	35 [0] (14.3) 2,786	40 [1] (15.6) 3,663	32 [0] (12.0) 3,447	47	20	42.6
b. Vergence and Accommodation (5-J5)	6 (2.2) 384	13 (3.7) 1,274	8 [1] (3.3) 389	9 [0] (3.5) 579	6 [0] (2.3) 432	13	4	30.8
c. Muscle Structure and Physiology (5-J6)	4 (1.5) 347	6 (1.7) 588	4 [0] (1.6) 417	4 [0] (1.6) 543	6 [0] (2.3) 703	9	3	33.3
SUBPROGRAM TOTAL	49 (18.3) 4,008	64 (18.1) 6,272	47 [1] (19.3) 3,592	53 [1] (20.6) 4,785	44 [0] (16.5) 4,582	69	27	39.1
6. Disorders (5-J7)								
a. Strabismus (5-J8)	9 (3.4) 618	24 (6.8) 2,352	10 [0] (4.1) 709	10 [0] (3.9) 900	23 [1] (8.6) 1,617	36	22	61.1
b. Motor Neuro-Ophthalmic Disorders (5-J9)	4 (1.5) 265	9 (2.5) 882	4 [0] (1.6) 350	6 [0] (2.3) 586	7 [1] (2.6) 754	15	6	40.0
SUBPROGRAM TOTAL	13 (4.9) 883	33 (9.3) 3,234	14 [0] (5.7) 1,059	16 [0] (6.2) 1,486	30 [2] (11.3) 2,371	51	28	54.9

UPDATED NATIONAL PLAN PROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

		Panel Rec.	Figures shown below are Number of Projects [New Mechanisms] (Percent of Projects in Program) Dollars in Thousands			Applications FY 1983-84		
	FY 1981	FY 1983	FY 1982	FY 1983	FY 1984	Received	Funded	Percent
Optics and Refractive Errors, Including Myopia (5-K1)								
7. Optics and Refractive Errors, Including Myopia (5-K1)	3 (1.1) 261	12 (3.4) 1,176	4 [2] (1.6) 427	5 [1] (1.9) 482	5 [1] (1.9) 634	8	5	62.5
PROGRAM TOTAL	268 (100.0) 22,070	353 (100.0) 34,594	244 [12] (100.0) 21,351	257 [8] (100.0) 24,972	266 [11] (100.0) 27,538	448	174	38.8

REVISED PROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
		Research Grants	Clinical Trials		
Visual Processing and Amblyopia (5-G1)					
1. Normal and Abnormal Development (5-G2)					
a. Molecular (5-G3)	19 [0] (7.1) 2,249	30 (8.5)	0 (0.0)	27 [2] (10.2) 3,452	24 [0] (9.0) 3,288
b. Cell and Systems (5-G4)	44 [1] (16.5) 4,669	52 (14.8)	0 (0.0)	32 [0] (12.1) 3,539	31 [0] (11.6) 3,406
c. Behavior (5-G5)	7 [1] (2.6) 664	10 (2.8)	0 (0.0)	11 [1] (4.2) 1,094	9 [0] (3.4) 884
SUBPROGRAM TOTAL	70 [2] (26.2) 7,582	92 (26.2)	0 (0.0)	70 [3] (26.4) 8,085	64 [0] (24.0) 7,578
2. Structure and Function (5-G6)					
a. Molecular (5-G7)	8 [1] (3.0) 907	17 (4.8)	0 (0.0)	9 [0] (3.4) 1,075	10 [0] (3.7) 1,1[illegible]
b. Cell and Systems (5-G8)	60 [2] (22.5) 6,830	67 (19.1)	0 (0.0)	55 [0] (20.8) 6,905	62 [0] (23.2) 7,944
c. Behavior (5-G9)	25 [2] (9.4) 2,238	26 (7.4)	0 (0.0)	23 [1] (8.7) 1,951	21 [1] (7.9) 2,088
SUBPROGRAM TOTAL	93 [5] (34.8) 9,975	110 (31.3)	0 (0.0)	87 [1] (32.8) 9,931	93 [1] (34.8) 11,176
3. Disorders (5-H1)					
a. Amblyopia (5-H2)	16 [1] (6.0) 1,610	23 (6.6)	10 (35.7)	17 [1] (6.4) 1,748	15 [0] (5.6) 1,756

REVISED PROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
		Research Grants	Clinical Trials		
b. Sensory Neuro-Ophthalmic (5-H3)	2 [0] (0.7) 257	10 (2.8)	0 (0.0)	2 [2] (.8) 509	3 [0] (1.1) 355
SUBPROGRAM TOTAL	18 [1] (6.7) 1,867	33 (9.4)	10 (35.7)	19 [3] (7.2) 2,257	18 [0] (6.7) 2,111
Ocular Motility and Strabismus (5-J1)					
4. Normal and Abnormal Development (5-J2)	4 [0] (1.5) 282	11 (3.1)	0 (0.0)	4 [0] (1.5) 493	4 [0] (1.5) 414
5. Structure and Function (5-J3)					
a. Conjugate Eye Movements (5-J4)	36 [0] (13.5) 3,791	41 (11.7)	0 (0.0)	38 [0] (14.3) 4,126	36 [1] (13.5) 4,135
b. Vergence and Accommodation (5-J5)	5 [0] (1.9) 370	14 (4.0)	0 (0.0)	5 [1] (1.9) 484	6 [0] (2.2) 537
c. Muscle Structure and Physiology (5-J6)	6 [1] (2.2) 694	8 (2.3)	0 (0.0)	3 [1] (1.1) 303	7 [2] (2.6) 655
SUBPROGRAM TOTAL	47 [1] (17.6) 4,855	63 (17.9)	0 (0.0)	46 [2] (17.4) 4,913	49 [3] (18.4) 5.327
6. Disorders (5-J7)					
a. Strabismus (5-J8)	23 [0] (8.6) 1,597	13 (3.7)	18 (64.3)	26 [0] (9.8) 1,66[illegible]	28 [0] (10.5) 2,023
b. Motor Neuro-Ophthalmic Disorders (5-J9)	7 [1] (2.6) 755	15 (4.3)	0 (0.0)	7 [2] (2.6) 668	5 [1] (1.9) 472

REVISED PROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

Figures shown below are
Number of Projects
(Percent of Projects in Program)

	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
SUBPROGRAM TOTAL	30 [1] (11.2) 2,352	28 (8.0)	18 (64.3)	33 [2] (12.5) 2,331	33 [1] (12.4) 2,495
Optics and Refractive Errors, Including Myopia (5-K1)					
7. Optics and Refractive Errors, Including Myopia (5-K1)	5 [1] (1.9) 634	14 (4.0)	0 (0.0)	6 [0] (2.3) 635	6 [0] (2.2) 607
PROGRAM TOTAL	267 [11] (100.0) 27,547	351 (100.0)	28 (100.0)	265 [11] (100.0) 28,645	267 [5] (100.0) 29,708

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VISUAL PROCESSING AND AMBLYOPIA

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Normal and Abnormal Development: Molecular

1

Perspective on Recent Research

This area of research has been and continues to be very active. New techniques from molecular biology are being developed and used in studies of the visual system. New discoveries on other parts of the nervous system are being applied to the visual system and new investigators are increasingly being drawn to questions within this area.

Progress has been made in identifying molecules transported down the optic nerve, understanding the development of synaptic transmitters within the visual cortex, understanding the development of synapses within the retinotectal system, and determining the existence of factors which assist regeneration of the optic nerve.

These topics are of fundamental long-term importance. Regeneration of nerves within the visual system and understanding the molecular basis of the changes that underlie amblyopia are the goals of most projects.

Progress in Areas Discussed in The 1983-1987 Plan

The first Program Development Priority of this subprogram (DI) is to study the development of the visual system at the molecular level using animal models. Two molecules have been identified that may play a role in the processes by which cells in the visual system contact each other. One is called CAM (for cell adhesion molecule), and antibodies to it disrupt connections in the retinotectal system.[1,2] The other is called TOP (for topographic), and it has a marked gradient across the dorsoventral axis of the retina in birds.[3]

The second Program Development Priority is to analyze the effects of visual deprivation at the molecular level. When the Plan was written, the hypothesis that catecholamines affect plasticity in the cat visual cortex was prominent. Work in several laboratories has since thrown doubt on this hypothesis,[4] while other new studies have presented evidence in support of it.[5] The hypothesis is an important one, and work must continue until its truth or falsity is clearly established. Suggestions have been made that other substances such as acetylcholine or serotonin might affect plasticity. However, it remains possible that the crucial factor is not a conventional transmitter at all, but some entirely different molecule(s).

Significant progress has also been made in the area categorized in the Plan as the Program Base: studies of factors for regeneration of pathways in the central nervous system (CNS). Various nerve growth factors appear to have effects not only on the peripheral nervous system, but on the central nervous system as well.[6] Another area of intensive research is to examine the role of glycoprotein(s) and the extracellular matrix in the process of regeneration. One approach has been to use antibodies such as N-CAM as substrate to stimulate regeneration in both in vivo and in vitro experiments.[1,7]

A most striking demonstration of the competence of even adult retinal ganglion cells to regenerate an injured axon is the recent observation that adult rat retinal ganglion cells will regenerate axons for distances of several centimeters when they have been provided with a segment of peripheral nerve that has been grafted into the retina.[8] This observation shows that peripheral nerve contains the necessary factors for regeneration that are not normally available to CNS neurons. These factors may include a suitable substrate over which to grow, as well as substances which serve to induce the alterations in gene expression that are necessary for axon growth. Both the molecular[9] and cellular[10] requirements for an appropriate substrate for growth of ganglion cell axons have been further defined.

New and Developing Areas of Research

Considerable evidence suggests that changes in neuronal gene expression are also necessary for successful axon growth, because certain proteins (called "growth associated proteins," or GAPs) are synthesized in greater quantities during periods of axon growth. Candidates for the signals that regulate these changes in gene expression are polypeptides that are released by supporting cells of the peripheral nerve distal to the point of injury.[11] Furthermore, in the insect nervous system, certain antigens are transiently expressed, as a growth cone contacts specific axons during the growth toward its target.

Several laboratories are working on regeneration in the central visual pathways and this area holds substantial promise both in terms of our understanding of basic mechanisms and for potential clinical applications.

New growth factors and proteins are continually being identified, and each has to be evaluated in terms of its basic mechanism of action and role in the development of the visual system. Preliminary evidence suggests that a large change in the layering pattern of some synaptic transmitters occurs during the first few postnatal weeks in the kitten,[12] and the function of this change needs to be understood.

The sequential introduction of three neurofilament polypeptides into ganglion cell axons during development has also been reported: the polypeptide which crosslinks the neurofilaments appears only very late (12 days postnatal in the rabbit). Axonal transport of neurofilaments slows by a factor of about 8 in rabbit retinal ganglion cells during early postnatal development.[11]

Balance of Effort Within Subprogram

Although the Plan recommended that NEI research support in this subprogram be increased from 19 in FY 1981 to 25 in FY 1983, the number of grants awarded has remained essentially constant since FY 1981. However, many investigators are beginning to include molecular work in projects that are primarily concerned with cellular and systems questions, so the number of grants categorized in this subprogram may underepresent the amount of work actually being carried out in the area.

The search for factors that would help the regeneration of the optic nerve and other components of the visual pathway is an area that the Plan lists as the Program Base and recommends for level funding because it was considered to be adequately supported in FY 1981. Subsequent to that recommendation, the number of grants funded in this area dropped from 9 in FY 1981 to 4 in FY 1984. At the same time new opportunities have arisen. As described above, some success has been obtained with the regeneration of neurons in the visual system, and there is increasing evidence that neurons will regenerate within other areas of the central nervous system. For these reasons the Evaluation Panel recommends that the search for regeneration factors be made a Program Development Priority.

Investigations of the development of the visual system and of the effects of visual deprivation at molecular levels are both identified by the Plan as Program Development Priorities. The number of grants funded for research on the development of the visual system remained static between FY 1981 and FY 1984 at 6, whereas the number of grants funded on visual deprivation increased from 4 to 8 during that period.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

Each of the three categories comprising the Plan's Program Base and Program Development Priorities continues to be highly relevant today. Moreover, important new discoveries in neural regeneration give added importance to the Program Base category.

The specific research opportunities identified in the Plan continue to be promising. These include: the identification of molecules transported down the axon, the identification of cell surface markers in the retinotectal system, the measurement of changes in proteins during development, and the acceleration of regeneration of optic nerve axons in lower vertebrates by nerve growth or other factors. Whether catecholamines, other transmitter substances, glycoproteins, or other molecules affect the critical period for the development of connections in the visual cortex is also important.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends that the Priorities including molecular investigation of normal development (Dl) and the effects of visual deprivation (D2) remain Program Development Priorities. New technologies are available, and there is the prospect of eventual rewards if the basic mechanisms can be understood. In view of new research opportunities the Panel recommends that the Program Base category describing research in regeneration of optic nerve and central visual pathways be moved into the Program Development Priorities. A reanalysis of the FY 1984 grants funded in this and the following subprogram, Cell and System, resulted in shifts between and within these subprogram reflecting a net gain of one grant, for a total of 19 for the Molecular subprogram. We recommend an increase of 11 grants, bringing the total number of funded grants in this subprogram to 30.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: NORMAL AND ABNORMAL DEVELOPMENT, MOLECULAR (5-G3)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Search for factors for regeneration of optic nerve and other components of the visual pathways. (B1)	9	9	4 [1]	4	4	13	3	23.1
TOTAL FOR PROGRAM BASE	9	9	4 [1]	4 [0]	4 [0]	13	3	23.1
PROGRAM DEVELOPMENT PRIORITIES								
1. Investigate development of the visual system at the molecular level using animal models. (D1)	6	10	6	5	6	12	3	25.0
2. Analyze the effects of visual deprivation/abnormal stimulation at molecular levels. (D2)	4	6	3	5 [1]	8	11	6	54.5
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	10	16	9 [0]	10 [1]	14 [0]	23	9	39.1
TOTAL FOR SUBPROGRAM	19	25	13 [1]	14 [1]	18 [0]	36	12	33.3
(% OF PROGRAM)	(7.1)	(7.1)	(5.3)	(5.4)	(6.8)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: NORMAL AND ABNORMAL DEVELOPMENT, MOLECULAR (5-G3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Investigate development of the visual system at the molecular level using animal models. (D1)	SAME	8	12	0	14 [1]	10
2. Analyze the effects of the visual deprivation a abnormal stimulation at molecular levels. (D2)	SAME	9	10	0	10	8
3. Search for factors for regeneration of optic ne other components of the visual pathways. (D3)	MOVED (WAS B1)	2	8	0	3 [1]	6
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		19 [0]	30	0	27 [2]	24 [0]
TOTAL FOR SUBPROGRAM		19 [0]	30	0	27 [2]	24 [0]
(% OF PROGRAM)		(7.1)	(8.5)	(0.0)	(10.2)	(9.0)

Normal and Abnormal Development: Cell and Systems

2

Perspective on Recent Research

This continues to be a major area of research, both in terms of the number of grants and scientific advances. Studies of normal development in the embryo and during the postnatal period have provided new insights into mechanisms of cell segregation and synapse formation. The discovery of a simple animal model to produce ocular dominance columns has opened the possibility for a more direct examination of underlying factors. The use of intracellular methods to label neurons in the central visual pathway of normal and visually deprived animals has made it possible to describe the effects of visual deprivation at a cellular level. The realization that, at least in lower vertebrates, neural connections can be broken and formed by different experimental manipulations has led to a reexamination of the conditions for synaptic stability and modulation. The role of activity in the process of innervation and for the maintenance of synaptic connections is beginning to be more fully appreciated.

These new technical developments and experimental discoveries indicate the strength and opportunities in this area of research. The recent work has further improved our understanding of the cellular basis of blindness caused by strabismus, congenital cataracts, and other forms of visual deprivation in children.

Progress in Areas Discussed in The 1983-1987 Plan

There have been significant advances made in several areas related to normal development, primarily with the help of new anatomical and physiological tools. Prenatal studies in the cat and monkey have shown that cells in the lateral geniculate body initially receive binocular inputs, a phase followed by laminar segregation of monocular cells. The sequence of events does not occur if one eye had been removed earlier, indicating that the process of segregation depends on an interaction between the inputs from the two eyes.[1,2] In addition, evidence has been presented that activity is important for segregation and the formation of patterned connections; experiments showed that the formation of ocular dominance columns in the cat striate cortex did not occur when the optic nerves were blocked by TTX.[3] The effects of visual deprivation on a cellular level have begun to be explored by doing intracellular labelling of neurons with horseradish peroxidase (HRP) and reconstructing the neurons and their axonal projections in cats raised with monocular occlusion.[4,5] So far only the dorsal lateral geniculate body has been examined, but already at this level there have been reports of dramatic differences in the retino-geniculate innervation between the normal and deprived animals.

Studies of the retinotectal system in lower vertebrates remains an area of great interest because of the possibility of regeneration and formation of new neurons. Some recent experiments on this system illustrate the differences between regeneration in a system and the initial development of that system.[6] Others demonstrated how nerve cells may change their connections to give appropriate responses when rearrangements over short distances and long periods of time are adequate.[7] The formation by experimental manipulation of ocular dominance columns which are normally not present in the tectum has begun to be used to study the mechanisms underlying the segregation of different input.[8] Another promising approach to study innervation selectivity that has emerged in recent years is transplantation of neural tissue into different regions of the visual pathway.[9] Finally, the possibility of regeneration within the CNS is being investigated with new vigor. Recent experiments indicate that under appropriate conditions regeneration can indeed be observed in CNS pathways.[10]

New and Developing Areas of Research

Although a number of questions concerning the anatomical and physiological mechanisms underlying the effects of visual deprivation remain to be answered, the emphasis has begun to shift toward molecular approaches. It seems likely that in the future molecular tools will be used more often in combination with the more traditional morphological and physiological techniques. From a clinical point of view it would be helpful if the paradigms of visual deprivation used in animal experiments could be more tuned to conditions producing deficits similar to those observed in patients. This should contribute to the development of improved methods to prevent and treat amblyopic patients.

Balance of Effort within Subprogram

From FY 1981 to FY 1984 the number of funded grants in this subprogram concerned with development of the visual system (Bl) increased from 25 to 32, while those concerned with the effects of visual deprivation (B2) decreased from 26 to 14, which represents a clear shift from equal distribution between the two areas in the preceding years. This change may indicate increased interest in learning more about normal development before attempting to assess the effects of visual deprivation.

Both these areas of research are in the Program Base and the Plan recommends a moderate decrease in the number of funded grants to 22 for each by FY 1983. Because the funding rate in the two categories has been about the same, the change in the number of funded grants from FY 1981 to FY 1984 reflects the relative number of quality grant applications received for research in each area. This demonstrates the natural evolution of the field.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The Plan regarded this subprogram as very strong and the level of activity was considered more than adequate. In fact, the Panel recommended a reduction in the number of grants from 51 in FY 1981 to 44 in FY 1983. All grants were categorized as being part of the Program Base because there appeared to be no unexplored research opportunities in terms of new methods or insights.

In the years to come this area of research will continue to be of crucial importance for our understanding of strabismic amblyopia and other conditions caused by visual deprivation. The work also should provide insights into prevention and the development of new methods of treatment.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends that the two research categories in this subprogram remain in the Program Base. The reanalysis of FY 1984 grants, noted in the previous chapter, resulted in a net loss of two grants from this subprogram. One grant was shifted to Normal and Abnormal Development: Molecular; the other was reclassified under Structure and Function, Cell and System, Chapter 2B. In view of the substantial progress indicated above, a modest increase of four additional grants, bringing the total to 36, is recommended for studies of normal development. An additional two grants, bringing the total to 16, is recommended for the effects of visual deprivation.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: NORMAL AND ABNORMAL DEVELOPMENT, CELL AND SYSTEMS (5-G4)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Investigate development of the visual system at cell and systems levels using animal models. (B1)	25	22	26 [1]	30	32 [1]	50	20	40.0
2. Analyze the effects of visual deprivation/-abnormal stimulation at cell and systems level. (B2)	26	22	19	21	14	14	6	42.9
TOTAL FOR PROGRAM BASE	51	44	45 [1]	51 [0]	46 [1]	64	26	40.6
TOTAL FOR SUBPROGRAM	51	44	45 [1]	51 [0]	46 [1]	64	26	40.6
(% OF PROGRAM)	(19.0)	(12.5)	(18.4)	(19.8)	(17.3)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: NORMAL AND ABNORMAL DEVELOPMENT, CELL AND SYSTEMS (5-G4)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Investigate development of the visual system at the and systems levels using animal models. (B1)	SAME	33 [1]	36	0	23	22
2. Analyze the effects of visual deprivation and a stimulation at cell and systems levels. (B2)	SAME	11	16	0	9	9
TOTAL FOR PROGRAM BASE		44 [1]	52	0	32 [0]	31 [0]
TOTAL FOR SUBPROGRAM		44 [1]	52	0	32 [0]	31 [0]
(% OF PROGRAM)		(16.5)	(14.8)	(0.0)	(12.1)	(11.6)

Normal and Abnormal Development: Behavior

3

Perspective on Recent Research

The accomplishments in studying animal models of visual development, especially those involving abnormal visual experience,[1-3] have contributed immensely to the clinician's understanding of the conditions he or she encounters in patients.[4-6] Although only preliminary work has been done on animal models at the behavioral level, the Panel continues to regard this as an important area of study.

Although no specific changes in diagnosis or therapy of the human condition have directly resulted from these animal models, they have, by introducing the concept of the "critical period" of visual development, made clinicians more conscious of the importance of early diagnosis and treatment in their patients and have led to a surge of interest in the study of early visual development in infants.[7-11]

Clinical work in this area has largely concentrated on the study of the development of the visual system in normal human infants using noninvasive methods. The preferential looking technique has been the most widely used methodology, and this has been combined with a variety of new computer techniques for stimulus generation.

Progress in Areas Discussed in The 1983-1987 Plan

Overall progress in the two areas designated as Program Base in the Plan has been steady, if not spectacular. In particular, attempts to use noninvasive methods to achieve estimates earlier in life of the development of human visual functions have continued to be at the forefront of research in this subprogram. These research efforts, focused as they are in areas where animal modeling of visual deprivation has provided new insights into visual development, have lived up to the expectations of the Plan.

Recent clinical studies have concerned themselves with the development of grating acuity, vernier acuity, stereo acuity, anisometropic resolution, and color vision in human infants. Several workers have shown that vernier acuity consistently exceeds grating acuity, and that both develop rapidly during the first six months of life.[12-13] It seems likely that age norms for vernier acuity in infants similar to those for contrast sensitivity[14] will soon be established.

In studies of color vision in infants it has been shown in preferential looking (PL) experiments that newborns can discriminate between colored and grey checkerboards.[15] Further, also by PL experiments, it has been shown that two separate receptor types and chromatic pathways are functional by the fifth week of postnatal life, and that one of these pathways must contain information from short wavelength cones.[16,17] There is also some indication that the development of the blue-yellow pathways lag behind the red-green pathways.[18]

New and Developing Areas of Research

Although the development of exciting new areas of research within the subprogram does not appear at this time to be highly likely, nevertheless, the efforts of investigators to extend their laboratory observations with variants of the techniques of forced-choice preferential looking to the clinic are important.[19] If successful, this would bring clinicians closer to the goal of being able to quantify visual acuity and other functions in infants and small toddlers—something not heretofore possible.

Balance of Effort Within Subprogram

This subprogram has a long and stable history within the overall NEI research funding effort. The Panel's review of the grant applications received and approved by NIH but not funded revealed that they were of high quality and overall relevant to the subprogram's objectives. These were not funded because of the extraordinary competition among quality applications for limited research funds.

The vast majority of funded research in this subprogram is research directed toward Program Base category B2, which concerns studies of the development of the visual system of infant humans by noninvasive methods. All of this research is well grounded and likely to be productive within the lifetime of the Plan.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

In the light of the preceding discussion, the Plan's recommendations for the Program Base in this subprogram seem appropriate as far as this subprogram's overall growth and future is concerned. The careful application of laboratory-gained knowledge, both in developmental animal and human psychophysics, to the clinic is the major area of progress expected in this subprogram.

Recommended Changes in Program Base and/or Program Development Priorities

Although dramatic growth within the subprogram is not expected in the near future, the Panel believes that a modest increase in the seven grants funded in FY 1984 to a total of ten in FY 1987 would be desirable. The Panel recommends combining the two recommendations pertaining to animal models (B1) and (D1) into one Program Base category and to retain the existing Program Base category (B2) but in a shortened form. This reflects the need at this time to combine the nascent discipline of animal behavioral research in applied psychophysics with the more developed infant human psychophysics research effort. The two disciplines would, in fact, become parallel tracks of the same effort and it is to be hoped that investigators in both fields develop significant cooperation among themselves.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: NORMAL AND ABNORMAL DEVELOPMENT, BEHAVIOR (5-G5)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM BASE								
1. Analyze the effects of visual deprivation/-abnormal stimulation at the behavioral level. (B1)	5	6	3	1	0	2	0	
2. Study development of visual systems of infant humans by developing noninvasive methods to follow the clinical course of disorders after attempts at medical or surgical intervention. (B2)	6	7	6	9 [1]	7 [1]	10	7	70.0
TOTAL FOR PROGRAM BASE	11	13	9 [0]	10 [1]	7 [1]	12	7	58.3
PROGRAM DEVELOPMENT PRIORITIES								
1. Investigate development of the visual system at the behavioral level using animal models. (D1)	1	3	1	0	0	2	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	3	1 [0]	0 [0]	0 [0]	2	0	0.0
TOTAL FOR SUBPROGRAM	12	16	10 [0]	10 [1]	7 [1]	14	7	50.0
(% OF PROGRAM)	(4.5)	(4.5)	(4.1)	(3.9)	(2.6)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: NORMAL AND ABNORMAL DEVELOPMENT, BEHAVIOR (5-G5)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Investigate development of the visual system at the cell the behavioral level using animal models, including the effects of abnormal stimulation. (B1)	COMBINES OLD B1, D1	0	2	0	3 [1]	2
2. Study development of the visual system of human infants using noninvasive methods. (B2)	SHORTENED	7 [1]	8	0	8	7
TOTAL FOR PROGRAM BASE		7 [1]	10	0	11 [1]	9 [0]
TOTAL FOR SUBPROGRAM		7 [1]	10	0	11 [1]	9 [0]
(% OF PROGRAM)		(2.6)	(2.8)	(0.0)	(4.1)	(3.4)

Structure and Function: Molecular

4

Perspective on Recent Research

The knowledge of the biochemical and molecular specificity of the central visual system is still very rudimentary in spite of clear progress during the last few years. The neurotransmitters used in the retina-geniculo-cortical pathway are still unknown and their identification remains a major challenge in the field. Similarly, the chemical signals used by the different cortical cells are largely not known. Though progress has been made with the identification and localization of peptidergic neurons at various levels in the visual system and in some cases the co-localization with classic neurotransmitters. The search for cell-specific markers using specific markers using monoclonal antibodies is still at an early stage but has had a promising start.

Progress in Areas Discussed in The 1983-1987 Plan

A technical advance has been the development of a monoclonal GABA antibody which now is commercially available and gives very consistent labelling. The antibody against glutamic acid decarboxylase (GAD) has previously been the preferred means to demonstrate GABAergic neurons. Also available are antibodies against a number of peptides, some of which label cells in the cat and monkey visual cortex. By doubling labeling procedures it has been shown that nearly all cells stained immunocytochemically for somatostatin (SRIF), neuropeptide Y(NPY), and cholecystokinin octapeptide (CCK) also stained with GAD antibody. All GABAergic cells did not, however, label with the different antibodies against peptides.[1] In addition, it has been shown that 80 percent of the cells in the rat cortex labelled with an antibody against cholineacetyltransferase (Chat) also showed immunoreactivity for vasoactive intestinal polypeptide (VIP).[2] The functional role of these peptides and their interaction with the classic transmitter substances remain to be explored.

Several molecules concerned with axonal transport of the optic nerve have been identified. Some are heat shock proteins.[3] The developmental expression of the src gene product has also been studied.[4] Synapsin I and sodium-potassium ATP[5] have been shown to be transported rapidly and biphasically in retinal ganglion cells, indicating that they are released from two separate pools in the cell body. The axons of retinal ganglion cells contain a form of certain neurofilament proteins that is antigenically distinct from the form in the cell body, indicating that these proteins are specifically modified (probably phosphorylated) for their axonal function.

The identity of the main transmitters used in the signaling of information from the retina to the various visual centers and to the cortex still remains to be discovered. The nonspecific innervation of the visual cortex by noradrenergic and serotonergic fibers has been described in several species.[6] Evidence has been presented that aspartate or glutamate may be the transmitter of layer 6 cells in the projection to the lateral geniculate body.

A great deal of new information has been obtained about gamma-aminobutyric acid (GABA), the main inhibitory transmitter in the central visual pathway. According to not-yet-published studies the number of GABAergic cells appears to be around 25-30 percent of the total neuronal population in the monkey striate cortex—up from the earlier figures of 8 to 15 percent. It has recently been demonstrated that nearly all cells stained by antibodies against CCK (cholecystokinin octapeptide). SRIF- (somatostatin) and NPY- (neuropeptide Y) labeled cells are also immunoreactive to glutamic acid decarboxylase (GLUDase). However, not all GABAergic cells show co-localization with a neuropeptide.[2] The neuropeptides are thought to function as modulators rather than regular transmitter agents. The wealth of information available about the anatomy and physiology of the visual cortex makes this a very suitable tissue in which to put concepts of modulatory action into a functional setting. Techniques have also become available to study binding of transmitters to postsynaptic cells.[7] The identification and localization of different receptors and the use of various agonists and ligands will probably become increasingly important in the study of the chemical signaling in the visual system.

Another area of increased activity is in the search for cell-specific markers using the monoclonal antibody technique. The most striking finding to date in the central visual pathways has been a monoclonal antibody (Cat-301), first isolated from the spinal cord, that preferentially labels cells in the magnocellular layers of the monkey lateral geniculate body.[8] The same antibody appears also to stain selectively the "blobs" in the striate cortex. There is evidence that Cat-301 stains Y-cells in the cat lateral geniculate body. In a different study antiserum was made against retinal ganglion Y-cells and an attempt was made to kill such cells selectively.[9] The initial enthusiasm over the monoclonal antibody technique has been somewhat modified with the realization that few of the obtained antibodies are of great interest and that the screening and characterization of the antibodies is a labor-intensive task. Nonetheless, when properly used the technique remains a most powerful research tool that is sure to yield new and important information about the visual system at the molecular level.

New and Developing Areas of Research

As work on the anatomy and localization of synaptic transmitters in the central visual system continues, research on their function should also be done. Only the function of GABA is clearly understood. Why two putative transmitters should exist in the same neuron is mysterious, as is the rationale for the modulatory actions of some conventional transmitters as well as the peptides. Some pointers can be obtained from experiments done on the hippocampus and sympathetic ganglia.[10-12] The wealth of information available about the anatomy and physiology of the visual cortex make this a very suitable tissue in which to put the concepts of modulatory action into a functional setting. This is clearly an area that warrants continued emphasis for imaginative but solid research grant proposals.

Balance of Effort Within Subprogram

The Plan recommends an increase in this subprogram from 6 grants funded in 1981 to 17 by FY 1983. However, by FY 1984 only 9 grants had been funded. Therefore, there has been modest growth in this subprogram which is projected in the Plan for rapid expansion. The areas identified as particularly promising are the identification and localization of transmitters in the visual system, the function of monoamines and peptides as modulators of synaptic action, the use of markers of cell function and development history, and the study of axonal transport. Recent developments in monoclonal antibodies and tissue culture techniques are cited in expectation of a substantial increase in activity.

Specifically, the Plan recommends an increase from 3 grants in FY 1981 to 9 in FY 1983 on the identification of neurotransmitters, peptides, and other chemicals important in signaling. Seven grants were funded in FY 1984. The Plan also recommends an increase from 3 grants to 8 for the identification of molecules involved with cell specificity and function. It is disappointing that only 2 grants were funded in this category in FY 1984, given the rapid advances that are occurring in this area in research on tissues outside the visual system.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The Panel believes that the current Program Development Priorities continue to be appropriate and require only a slight modification in wording.

Recommended Changes in Program Base and/or Program Development Priorities

Because the Panel considers that the function of neurotransmitters should also be emphasized, it recommends that the wording of DI be changed.

The Panel believes that the identification of molecules involved with cell specificity and function (D2) should continue to be a priority.

In view of the continued promise of the molecular approach, the Panel recommends that both areas of research remain as Program Development Priorities. A reanalysis of grants classified in the various subprograms of Strabismus, Amblyopia, and Visual Processing resulted in some shifts within this subprogram and between this subprogram and others. Two grants were transferred from this subprogram to Structure and Function: Cell and Systems and one grant was added from Ocular Motility and Strabismus, Normal and Abnormal Development for a net loss of one grant (8 rather than 9).

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: STRUCTURE AND FUNCTION, MOLECULAR (5-G7)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
				[No. R03, R43, R44 in brackets]				
PROGRAM DEVELOPMENT PRIORITIES								
1. Identify neurotransmitters, peptides, and other chemicals important in signaling between cells in the visual pathways. (D1)	3	9	5	6	7 [1]	7	5	71.4
2. Identify molecules involved with cell specificity and function. (D2)	3	8	3	3	2	1	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	6	17	8 [0]	9 [0]	9 [1]	8	5	62.5
TOTAL FOR SUBPROGRAM	6	17	8 [0]	9 [0]	9 [1]	8	5	62.5
(% OF PROGRAM)	(2.2)	(4.8)	(3.3)	(3.5)	(3.4)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: STRUCTURE AND FUNCTION, MOLECULAR (5-G7)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM DEVELOPMENT PRIORITIES						
1. Identify, characterize, and define the function of neurotransmitters, peptides, and other chemicals important in signaling between cells in the visual pathways. (D1)	EXPANDED	7 [1]	10	0	8	9
2. Identify molecules involved with cell specificity and function. (D2)	SAME	1	7	0	1	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		8 [1]	17	0	9 [0]	10 [0]
TOTAL FOR SUBPROGRAM		8 [1]	17	0	9 [0]	10 [0]
(% OF PROGRAM)		(3.0)	(4.8)	(0.0)	(3.4)	(3.7)

Structure and Function: Cell and Systems

5

Perspective on Recent Research

This subprogram comprises the largest group of research projects within the Strabismus, Amblyopia, and Visual Processing Program. This is an area of remarkable strength and breadth and much new information has been obtained using new and powerful anatomical and physiological techniques.

Progress in Areas Discussed in The 1983-1987 Plan

Advances have been made in several areas but only a few examples will be given here. Our understanding of the functional organization of the monkey striate cortex has been significantly advanced by the use of a metabolic marker called cytochrome oxidase.[1] Several laboratories have since observed "blobs" (also called "puffs") of cytochrome oxidase staining in layers 2 and 3. The blobs receive direct geniculate input from the interlaminar layers of the lateral geniculate body[2] and show enhanced staining with antibody against gammabutyric acid decarboxylase.[3] Cells in the blob area respond selectively to color.[4]

The technique of labeling cells intracellularly with horseradish peroxidase is being used increasingly to study the microcircuitry of the cat and monkey visual cortex.[5,6] Similarly, the slice preparation has been used to analyze circuitry of cells previously labeled retrogradely by fluorescent markers.[7]

Studies of the monkey extrastriate areas have presented striking correlations between psychophysical phenomena and single cell responses.[8] This approach involves the analysis of single cell responses in the wide awake monkey with implanted electrodes. For example, in such a preparation it has been possible to study the role of attention on cellular responses in the infratemporal and parietal lobe.[9,10] It has been known for a number of years that neurons in the middle temporal visual area (MT) of the Macaque monkey respond vigorously to a given direction of a stimulus movement; recently it has been shown in a behavioral study that a lesion localized to MT caused deficits in the control of eye movement.[11]

New and Developing Areas of Research

Important advances have been made in studies of the functional organization of the higher visual centers. This has been made possible through the development of new anatomical methods which have been used with physiological recordings. This work represents a natural extension of previous studies rather than a new departure. An approach not yet fully appreciated in the Plan is brain slice preparation. This in vitro method is well suited for electrophysiological and pharmacological studies analyzing cellular connectivity. Physiological studies in behaving monkeys with implanted electrodes constitute a research area of growing interest perhaps because of the opportunity to correlate psychophysics with single cell responses. An approach of great current interest is to record single unit activity with many electrodes in behaving monkeys. This requires very sophisticated instrumentation and computer analysis but would make possible an important new dimension of analysis. Finally, this method of optical recording is being used for in vivo studies and several laboratories are beginning to use this approach in studies of the mammalian visual cortex.

Balance of Effort Within Subprogram

The Plan puts all research activity in this subprogram in the Program Base and recommends essentially continuing the level of support at the FY 1981 level of 62 grants through FY 1983. The number of funded grants in FY 1984 was 58, plus 2 Small Grants for Pilot Projects, with a funding rate of about 44 percent for FY 1984. Thus, the Plan's funding recommendations have been achieved in this subprogram.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The Panel views Program Base category B3, the analysis of the connections and functions of extrastriate areas, to be of special promise and to have unique opportunities to provide information about higher visual functions.

Program Base category Bl, concerned with investigation of cells in the visual pathway, had 25 grants in FY 1981 and the Plan recommends 23 grants for FY 1983. Instead of a decrease, the FY 1984 column shows an increase to 31 grants, indicating a vigorous research interest. The other categories remained at about the same level of support, but the recommended increase of support for studies of the extrastriate cortex (B3) has not yet materialized. The Panel considers this area of special interest.

Recommended Changes in Program Base and/or Program Development Priorities

Because of the existence of new opportunities for productive research, the Panel recommends redesignating Program Base category B3 as a Program Development Priority. The other categories all represent very strong research areas in which excellent progress is being made, but in view of their current strong support they are recommended to remain in the Program Base.

A reanalysis of the grants classified in this and other subprograms of Strabismus, Amblyopia, and Visual Processing resulted in the transfer of 2 grants to the Conjugate Eye Movements subprogram and the addition of 1 grant from the Normal and Abnormal Development: Cell and Systems subprogram, and 2 grants from the Visual Processing and Amblyopia: Structure and Function, Molecular subprogram, for a gain of 1 grant. However, 1 additional grant classified in this subprogram was inadvertently overlooked in the original analysis. The addition of this grant brings the revised total for this subprogram to 60 rather than 58 research project grants plus 2 Small Grants

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: STRUCTURE AND FUNCTION, CELL AND SYSTEMS (5-GB)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Investigate cells in the visual pathways: Functional specialization and its relationship to structure and connectivity. (B1)	25	23	21	25 [2]	31 [1]	35	18	51.4
2. Elucidate the role of afferent and efferent pathways in processing visual information. (B2)	19	18	17 [1]	18 [1]	12 [1]	28	10	35.7
3. Map and analyze extrastriate cortical areas; relate single cell activity with behavioral responses. (B3)	8	11	8	7	5	8	3	37.5
4. Relate behavioral/physiological studies in animals to human psychophysical data; study human psychophysics as a guide to physiological studies. (B4)	10	9	9	8	10	9	4	44.4
TOTAL FOR PROGRAM BASE	62	61	55 [1]	58 [3]	58 [2]	80	35	43.7
TOTAL FOR SUBPROGRAM	62	61	55 [1]	58 [3]	58 [2]	80	35	43.7
(% OF PROGRAM)	(23.1)	(17.3)	(22.5)	(22.6)	(21.8)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: STRUCTURE AND FUNCTION, CELL AND SYSTEMS (5-GB)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Investigate the functional specialization of cells in the geniculostriate pathways and relate their function to their structure and connectivity. (B1)	MORE SPECIFIC	27 [1]	33	0	26	30
2. Elucidate the role of extrageniculate subcortical regions in processing visual information. (B2)	MORE SPECIFIC	11 [1]	12	0	10	11
3. Relate psychophysical data in humans with behavioral and physiological findings in animals and study human pschophysics as a guide to physiological studies. (B3)	SAME (WAS B4)	12	12	0	10	11
TOTAL FOR PROGRAM BASE		50 [2]	57	0	46 [0]	52 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Analyze the connections and functions of extrastriate cortical areas. (D1)	MOVED, LESS SPECIFIC (WAS B3)	10	10	0	9	10
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		10 [0]	10	0	9 [0]	10 [0]
TOTAL FOR SUBPROGRAM		60 [2]	67	0	55 [0]	62 [0]
(% OF PROGRAM)		(22.5)	(19.1)	(0.0)	(20.7)	(23.2)

Structure and Function: Behavior

6

Perspective on Recent Research

Work in this area is largely concerned with basic psychophysical research including color and motion vision, studies of hyperacuity, visual masking, grating acuity, and statistical studies of the psychophysical function, to mention but a few of the research topics.

Taken together, these topics constitute a significant portion of visual psychophysical studies which have relevance for amblyopia. Considerable attention has been focused on the extrafoveal retina both for its inherent interest in normal visual function and as a model for aberrant foveal development. Motion vision continues to be a focus of research because it forms a crucial link in visual tracking and foveation of images. Studies of hyperacuity have led to new tools for characterizing normal visual function and may find practical application in patients whose vision has been reduced by cataracts.

Progress in Areas Discussed in The 1983-1987 Plan

Work in this area continues along the lines envisioned in the Plan. This area of behavioral research is a spawning ground for more applied projects.

New and Developing Areas of Research

The Panel did not identify any new or developing areas of research.

Balance of Effort within Subprogram

Funding in this subprogram declined from 38 projects in FY 1981 to 27 in FY 1984, exceeding the Plan's projected recommendation for a reduction to 32 grants in FY 1983. Nonetheless, the Panel judged that this level of support was adequate.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The first Program Base category (Bl), concerning the channel hypothesis, seems to have served its usefulness and now appears to designate too specific a category of research. Priorities D2 and D3 are redundant because most projects address both visual processes and methods .

Recommended Changes in Program Base and/or Program Development Priorities

The Panel recommends that Program Base category Bl be eliminated and categories B2 and B3 be combined and be made less specific. The Panel also recommends moving two grants, originally classified in B3, to the Sensory Neuro-Ophthalmic Disorders subprogram. This results in 25 research project grants funded in FY 1984 rather than 27.

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: STRUCTURE AND FUNCTION, BEHAVIOR (5-G9)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Evaluate the "channel hypothesis" of human visual processing. (B1)	11	9	9	7	6	12	6	50.0
2. Delineate human visual processes in normal/-dysfunctional states. (B2)	12	11	12 [2]	14 [1]	17 [1]	29	8	27.6
3. Develop psychophysical and objective methods for studying human visual processes in normal/dysfunctional states. (B3)	15	12	9 [2]	4	4 [1]	21	4	19.0
TOTAL FOR PROGRAM BASE	38	32	30 [4]	25 [1]	27 [2]	62	18	29.0
TOTAL FOR SUBPROGRAM	38	32	30 [4]	25 [1]	27 [2]	62	18	29.0
(% OF PROGRAM)	(14.2)	(9.0)	(12.3)	(9.7)	(10.1)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: STRUCTURE AND FUNCTION, BEHAVIOR (5-G9)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Conduct visual psychophysical studies in humans and animal models. (B1)	LESS SPECIFIC (COMBINES B2, B3) [DELETED OLD B1]	25 [2]	26	0	23 [1]	21 [1]
TOTAL FOR PROGRAM BASE		25 [2]	26	0	23 [1]	21 [1]
TOTAL FOR SUBPROGRAM		25 [2]	26	0	23 [1]	21 [1]
(% OF PROGRAM)		(9.4)	(7.4)	(0.0)	(8.7)	(7.9)

Disorders: Amblyopia

7

Perspective on Recent Research

Though incorporating new research approaches,[1-3] the major thrust of this subprogram remains research into the clinical condition of amblyopia, its detection at the earliest age possible,[4] characterization of the various defects in vision subsumed under the rubric amblyopia,[5,6] improving methods of evaluating vision in infants and young children to better assess progress in the treatment of amblyopia[7] and, finally, deeper research into the newly discovered mechanisms of defect and distortion of vision in amblyopic eyes brought to light by recent research.[8,9]

Progress in Areas Discussed in The 1983-1987 Plan

Simple comparison of the recommendations contained in the Plan with recent accomplishments, both in respect to the number and character of the research efforts in this subprogram, reveals a good match between the two. For each of the Program Development Priorities highlighted in the Plan, solid research projects have been funded. Planning and execution have nicely complemented each other in this subprogram and continued progress in the remaining years of the Plan and beyond is to be expected.

New and Developing Areas of Research

Although no new major breakthroughs in research are expected at this time, the possibility remains in the field of amblyopia, where treatment has relied for so long on various forms of occlusion of the sound eye (a centuries-old therapy), that newer forms of treatment less potentially destructive of binocular cooperation than the patch will be developed. This should be a paramount goal of research in this subprogram and would be a major breakthrough if accomplished.

Balance of Effort Within Subprogram

A nice balance of effort between applied and basic research efforts has been achieved very much as anticipated in the Plan. Growth in funding, though not to the extent envisioned in the Plan, has been steady, reflecting the needs in this area of research. The lack of histological correlation from human material is one of the problem areas in amblyopia research. Much of the materials obtained is by chance rather than by any systematic effort in this regard. However, the panel recommends and encourages efforts of investigators in this regard since these materials are probably available in routine postmortems in any large hospital.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

In the context of the foregoing, the Plan's recommendations—all classified as Program Development Priorities—continue to be appropriate. One area which was discussed and emphasized by the Panel in its deliberations was the need to establish an ongoing dialogue between clinicians, psychophysicists with an interest in amblyopia, and animal modelers with a shared interest in this field. The mechanism for such a study group, and particularly its formal organization and funding, remains unclear; nevertheless, some sort of forum for cross-fertilization among the disciplines is required for future growth within the research field of amblyopia.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel has only minor changes to recommend in the priorities themselves. Particular emphasis should be given to research into methods of early amblyopia detection and pathophysiological mechanisms of amblyopia. Both areas seem ready for real development. In addition, 10 clinical trial grants are recommended to support multicenter controlled studies of the prevention and treatment of amblyopia.

Since no grant applications or research efforts in D4 were forthcoming in previous years, the Panel believed a more general statement of the research objective would elicit a more positive response. The combining of D5 and D6 reflects the Panel's emphasis on new ways of detecting, preventing, and treating amblyopia.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: DISORDERS, AMBLYOPIA (5-H2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1. Develop methods for large-scale screening of vision in very young children for detection of abnormalities at an early age. (D1)	2	3	1	1	2	14	1	7.1
2. Improve clinical methods for evaluating vision in young children to assess better the need for treatment of amblyopia and monitor treatment. (D2)	0	3	1	2	5	10	4	40.0
3. Characterize the nature of amblyopic vision; improve the classification of forms of amblyopia; determine the natural history of amblyopia. (D3)	6	9	10	7	7	13	2	15.4
4. Support efforts to obtain histopathologic correlation in amblyopia. (D4)	0	2	0	0	0	0	0	
5. Conduct investigations of new treatments for amblyopia. (D5)	0	3	0	0	0 [1]	4	1	25.0
6. Expand inventory of tests of visual function in amblyopia and other sensory disorders. (D6)	1	4	0 [2]	0	0	4	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	9	24	12 [2]	10 [0]	14 [1]	45	8	17.8
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Study possible anatomical and physiological mechanisms involved in amblyopia. (A1)	0	0	0	0	2	1	1	100.0
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	0	0	0 [0]	0 [0]	2 [0]	1	1	100.0
TOTAL FOR SUBPROGRAM	9	24	12 [2]	10 [0]	16 [1]	46	9	19.6
(% OF PROGRAM)	(3.3)	(6.8)	(4.9)	(3.9)	(6.0)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: DISORDERS, AMBLYOPIA (5-H2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop and evaluate methods for large-scale screening of vision in very young children for detection of abnormalities at an early age. (D1)	SAME	2	4	0	2	2
2. Improve clinical methods for evaluating vision in young children to assess better the need for treatment of amblyopia and to monitor treatment. (D2)	SAME	5	6	0	6 [1]	4
3. Characterize the nature of amblyopic vision, improve the classification of forms of amblyopia, and determine the natural history of amblyopia. (D3)	SAME	7	8	0	6	6
4. Study pathophysiological mechanisms involved in amblyopia. (D4)	LESS SPECIFIC	2	5	0	3	3
5. Improve means to prevent and treat amblyopia. (D5)	COMBINES OLD D5, D6	0 [1]	0	10	0	0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		16 [1]	23	10	17 [1]	15 [0]
TOTAL FOR SUBPROGRAM		16 [1]	23	10	17 [1]	15 [0]
(% OF PROGRAM)		(6.0)	(6.5)	(35.7)	(5.4)	(5.6)

Sensory Neuro-Ophthalmic Disorders

8

Perspective on Recent Research

In general there has been a paucity of research in the area of sensory neuro-ophthalmic disorders. In part this seems to be related to a lack of collaborative endeavors between clinical neuro-ophthalmologists and basic researchers. One potentially strong area of fruitful investigation is to combine new brain imaging techniques with more sophisticated psychophysical methods of assessing visual function to provide better clinical-pathological (and functional-anatomical) correlations in patients with higher level disorders of visual function.

Progress in Areas Discussed in The 1983-1987 Plan

The Panel did not identify any areas of significant recent progress in this subprogram.

New and Developing Areas of Research

New imaging techniques—Positron Emission Tomography (PET) scanning, and Magnetic Resonance Imaging (MRI) scanning—in combination with sophisticated psychophysical studies can be used to study acute visual deficits in patients with neuro-ophthalmic disorders as well as the ways that patients adapt to and recover from such lesions.[1] In combination with results from studies using laboratory animals, it should be possible to develop better means of analyzing the visual complaints of patients with lesions within the central visual pathways; of predicting the recovery of visual deficits resulting from neurological lesions; and, perhaps most importantly, to recommend specific therapies to optimize the use of residual visual function and enhance adaptive capabilities.

Balance of Effort Within Subprogram

No grants are currently being funded in the areas originally classified under sensory neuro-ophthalmology. Under the new classification, a few grants are shown as funded, but these were transferred from the Structure and Function: Behavior subprogram. The paucity of funding in sensory neuro-ophthalmology has led the Panel to expand and clarify the Program Development Priorities.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The Panel decided that the Plan's Program Development Priorities reflect too narrow a view of sensory neuro-ophthalmology and are too detailed and restrictive. For example, no emphasis is given to the study of disorders of higher visual function, including extrastriate vision, and "blind sight" is not reflected.

Recommended Changes in Program Base and/or Program Development Priorities

Based on the above considerations, the following new Program Development Priorities are suggested. First, the Panel believes it necessary to include a specific priority in which psychophysical techniques, in combination with brain-imaging techniques and other objective methods of visual function, would be developed and applied to the study of human visual processing in patients with neuro-ophthalmic disorders. In this area, there has been some research that has previously been categorized in Structure and Function: Behavior. However, only four such grants were funded in 1984 and the Panel believes that six would be appropriate for this very important research area.

The second Program Development Priority, relating to the study of investigations of optic nerve disease, has been reworded to emphasize the importance of inflammatory optic neuritis and especially to focus the research effort at the more basic aspects—immunology and molecular biology—of demyelination. The Panel recommends an increase of two grants from the FY 1984 level of zero.

The revised third Program Development Priority emphasizes the study of animal models of optic neuropathies. This priority also had no research grants funded in FY 1984, and the Panel recommends that at least two grants in this area should be funded.

The original DI is recommended for deletion because the Panel sees no immediate opportunity for such epidemiologic studies to be conducted.

This restructuring of the subprogram resulted in the transfer into it of 2 FY 1984 grants originally classified in the Visual Processing and Amblyopia: Structure and Function: Behavior subprogram.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: DISORDERS, SENSORY NEURO-OPHTHALMIC DISORDERS (5-H3)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM DEVELOPMENT PRIORITIES								
1. Conduct epidemiologic studies of optic neuropathies in the United States. (D1)	0	1	0	0	0	0	0	
2. Conduct investigations of optic neuritis, ischemic optic neuropathy, and amaurosis fugax. (D2)	0	3	1	1	0	5	0	
3. Develop animal models of optic neuropathies; correlate electrophysiology, psychophysics, and histopathology; test the role of nutritional deficiencies in optic nerve disorders. (D3)	1	4	0	0	0	1	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	1	8	1 [0]	1 [0]	0 [0]	6	0	0.0
TOTAL FOR SUBPROGRAM	1	8	1 [0]	1 [0]	0 [0]	6	0	0.0
(% OF PROGRAM)	(0.4)	(2.3)	(0.4)	(0.4)	(0.0)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

VISUAL PROCESSING AND AMBLYOPIA: DISORDERS, SENSORY NEURO-OPHTHALMIC DISORDERS (5-H3)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop and apply psychophysical techniques in combination with imaging techniques and other objective methods for studying human visual processes in neuro-ophthalmic disorders. (D1)	NEW, INCLUDES PART OF D3	2	6	0	2 [1]	3
2. Conduct investigations of optic nerve disease, especially the immunology and molecular biology of demyelination. (D2)	EXPANDED	0	2	0	0 [1]	0
3. Develop and study animal models of optic neuropathies. (D3)	LESS SPECIFIC	0	2	0	0	0
	[DELETED OLD D1]					
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	10	0	2 [2]	3 [0]
TOTAL FOR SUBPROGRAM		2 [0]	10	0	2 [2]	3 [0]
(% OF PROGRAM)		(0.7)	(2.8)	(0.0)	(0.8)	(1.1)

OCULAR MOTILITY AND STRABISMUS

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Normal and Abnormal Development

9

Perspective on Recent Research

Some, but not nearly enough, growth has been made in this very important suprogram. The Plan emphasizes the critical appraisal of animal models of amblyopia and strabismus and especially the use of models of visual deprivation in animals in the attempt to understand human amblyopia. This is one area in particular where interaction between the neurobiologist and the clinician to relate animal and human results is so necessary. Both the strengths and the limitations of animal models of strabismus and amblyopia must be recognized.

Emphasis must also be placed upon the normal and abnormal development of the conjugate ocular motor systems. Disorders here lead to disabling and common problems, the foremost of which is congenital nystagmus.

Progress in Areas Discussed in The 1983-1987 Plan

Some of the ocular motor consequences of visual deprivation on saccadic eye movement control have been delineated in recent experimental studies on the effects of lid closure in the monkey. The results, combined with single unit recordings, suggest that superior colliculus pathways for triggering saccades seem to be the most susceptible to visual deprivation.[1] This study is only the first to address specifically the neurophysiological basis for the ocular motor disorders related to visual deprivation. In fact, this is the first study in primates even to ask about the consequences of visual deprivation on the conjugate eye movement system. Some studies have been performed in cats, both on the effects of dark-rearing and strobe-illumination,[2,3] but the resulting abnormalities do not appear to be comparable to any of the known ocular motor abnormalities of human infants.

Progress has also been made in the recording of eye movements in infants and the patterns of development of eye-head coordination, saccade, and pursuit in normal infants are now being elucidated.[4] These studies attest to the ingenuity of investigators in this field and provide an important basis for further studies in infants with neuro-ophthalmologic disorders. It has become clear that ocular motor performance in infants is much better than had been suspected previously.

New and Developing Areas of Research

While there are no striking new techniques in this area, the sophisticated neurophysiological study of deprived animals is an important area of research.[1]

Balance of Effort Within Subprogram

The Plan recommends a considerable expansion of research in this area but it has not materialized. Seventeen grants were recommended, but only six were funded in FY 1984. Fortunately, three of the grants are in an important area—the oculomotor effects of visual deprivation.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The Panel believes that the Program Development Priorities in the Plan are too numerous, specific, and restrictive and therefore are in need of some condensation and generalization. We also believe it necessary to emphasize research into the development of the ocular motor system at a very basic level combining molecular, physiological, and anatomical approaches. We also think that there is need for an increase in research in the area designated as Program Base because knowledge of the effects of visual deprivation on eye movement is of crucial importance in understanding amblyopia and strabismus.

Recommended Changes in Program Base and/or Program Development Priorities

Changes are recommended in the Program Development Priorities. D2 is modified to emphasize evaluation of quantitative eye movements as the techniques are developed and made available. D6 has been modified and focused explicitly to emphasize the need to use available basic science techniques to better understand development of the ocular motor system. The other priorities (old Dl, D3, D4, and D5) were eliminated because of their narrowness and inclusion in other subprograms. As a result of this restructuring, 2 grants were transferred out, 1 to the Conjugate Eye Movements and 1 to the Visual Processing and Amblyopia: Structure and Function: Molecular subprogram. Increases in funding for the revised, more focused priorities are suggested.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: NORMAL AND ABNORMAL DEVELOPMENT (5-J2)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Continue studies on the oculomotor effects of visual deprivation and other abnormal visual stimulation. (B1)	2	3	2	2	3	2	2	100.0
TOTAL FOR PROGRAM BASE	2	3	2 [0]	2 [0]	3 [0]	2	2	100.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Determine the relationship between early abnormal visual environment and the risk of comitant strabismus, myopia, or loss of stereoacuity. (D1)	0	2	0	0	0	0	0	
2. Develop quantitative eye movement recording techniques on neonates and young children. (D2)	0	2	1	1	1	0	0	
3. Determine the frequency of temporary strabismus in neonates/normal establishment of fusion. (D3)	0	1	0	0	0	0	0	
4. Evaluate adaptive oculomotive plasticity to visual oculomotor disorders. (D4)	0	2	0	0	0	1	0	
5. Describe at cellular and subcellular levels the development of extraocular muscles/associated cranial nerves. (D5)	0	2	0	0	0	0	0	
6. Describe at molecular, cellular, and behavioral levels the development of the oculomotor system. (D6)	3	5	2	2	2	1	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	3	14	3 [0]	3 [0]	3 [0]	2	0	0.0
TOTAL FOR SUBPROGRAM	5	17	5 [0]	5 [0]	6 [0]	4	2	50.0
(% OF PROGRAM)	(1.9)	(4.8)	(2.0)	(1.9)	(2.2)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: NORMAL AND ABNORMAL DEVELOPMENT (5-J2)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM BASE						
1. Continue studies on the oculomotor effects of visual deprivation and other abnormal visual stimulation. (B1)	SAME	2	5	0	1	1
TOTAL FOR PROGRAM BASE		2 [0]	5	0	1 [0]	1 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Develop and evaluate quantitative eye movement recording techniques for neonates and young children. (D1)	EXPANDED (WAS D2)	1	2	0	1	1
2. Describe at molecular, physiological, and anatomical levels the development of the oculomotor system. (D2)	REWORDED (WAS D6) [DELETED OLD D1, D3, D4, D5]	1	4	0	2	2
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	6	0	3 [0]	3 [0]
TOTAL FOR SUBPROGRAM		4 [0]	11	0	4 [0]	4 [0]
(% OF PROGRAM)		(1.5)	(3.1)	(0.0)	(1.5)	(1.5)

Structure and Function: Conjugate Eye Movements

10

Perspective on Recent Research

This area of research has shown steady progress with both the continued application of traditional techniques and development of newer methodology. In particular, the combined use of focal neuron-specific lesions (with neurotoxic agents) and physiological recordings has allowed more precise functional-anatomical correlations in the ocular motor system.

Progress in Areas Discussed in The 1983-1987 Plan

Specific examples of progress include the beginning of the delineation of the cerebral and brainstem pathways controlling smooth pursuit, the discovery of the structures in the brainstem where the gaze-holding network or neural integrator is located,[1] a beginning of an understanding of the oculomotor functions of the basal ganglia[2], new information about the role of higher centers in control of saccadic eye movements[2], and the specific definition of the role of the pontine paramedian reticular formation in the generation of eye movements.[4]

For example, injections of neurotoxins have shown that the pontine paramedian reticular formation has structures important for both horizontal and vertical saccadic eye movements but, contrary to prior ideas, does not contain neurons that seem important for gaze-holding or the vestibulo-ocular reflex. In contrast, injections of neurotoxins within the medial vestibular nucleus and adjacent portions of the perihypoglossal nuclei markedly impair the animal's ability to hold eccentric positions of gaze (i.e., the neural integrator is disturbed).[1] Likewise, neurotoxic lesions in the dorsal lateral pontine nuclei (DLPN) have suggested that DPLN is involved in smooth pursuit eye movements and that it possibly is a relay between posterior cerebral cortical structures and the cerebellar structures important for the control of smooth pursuit.[5]

The role of the substantia nigra and superior colliculus in the generation of eye movements has been elucidated in the past few years, largely through the combined use of single unit recordings and injections of neurotransmitter antagonists or agonists. The inhibitory role of the substantia nigra upon the superior colliculus and its mediation by GABA has been well demonstrated and furthermore, from a functional viewpoint, the substantia nigra-superior colliculus pathway has been shown to be important in the generation of volitional eye movements to remembered target locations[2]. This ability may depend upon frontal lobe-caudate projections to this area and has obvious important functional and clinical implications for the higher level control of saccadic eye movements.

These studies are an important first step toward a better understanding of the hierarchical organization of voluntary saccadic eye movement control.

Similar strategies using neuronal toxins and single unit recordings have been applied to structures in the posterior portions of the hemispheres that may be related to smooth pursuit eye movements.[6] Likewise large gross surgical lesions have revealed that each cerebral hemisphere plays an important role not just in ipsilateral smooth pursuit but contralateral and vertical smooth tracking as well.[7]

New and Developing Areas of Research

The ability to make focal neuronal lesions allows one to examine the effects of destroying neurons without affecting passing fibers.[4] This powerful technique allows functional-anatomical correlations and has potential application to understanding the clinical manifestations of the various neuronal degenerative diseases where cells and not fibers tend to be affected. These experimental neuronal lesions are complementary to gross structural lesions involving both fibers and neurons; clinically, the latter are commonly the result of lesions due to trauma or ischemia.

Finally, the use of sophisticated training techniques in monkeys has allowed remarkable control over the animal's behavior so that the higher level, volitional control of eye movements can be understood.[3] For example, it is possible to train animals to look in opposite directions to target stimuli or to remembered locations of target stimuli. Combined with single unit recordings and lesion techniques, investigators can now probe the underlying physiology of the higher level control of voluntary eye movements.

Balance of Effort Within Subprogram

Funding of grants in the Program Base has been stable over the past few years and fortunately many of them are incorporating the new lesion techniques into their research protocols. In each of the areas of the Program Base there has been a relatively even amount of funding and approval of grants. Increased funding of grants in the Program Development Priorities, however, has not taken place and the number of submissions has been small. Fortunately, work in category Dl—sensorimotor plasticity—is included in many of the research grants in the Program Base, as well as in the intramural program of the NEI. Category D2—neurotransmitters and chemicals—is, however, in need of more submissions and funding in spite of some work being performed intramurally.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The current recommendations aim to encourage and assist the evolution of the Program Development Priorities as well as maintain the momentum in the research areas of the Program Base. The thrust here is to emphasize and encourage the approaches of the molecular biologist as well as the neurophysiologist for ocular motor research. In general, these remain adequate and relevant, but some rewording is needed.

Recommended Changes in Program Base and/or Program Development Priorities

The Evaluation Panel believes it reasonable to shift one of the Program Development Priorities, D2, which is concerned with clinical problems, to the Motor Neuro-Ophthalmic Disorders subprogram (See Chapter 10). It is also necessary to rewrite the priority concerning the effects of drugs and neurotransmitters (D3) to emphasize the more fundamental question of the functions of neurotransmitters and neuropeptides and other chemicals important in the oculomotor systems, rather than simply just studying the influence of drugs on neurotransmitters. Though there were no NEI-funded extramural projects in this category in FY 1984, there has been some work in this area in the NEI intramural program. Similarly, the Program Development Priority relating to oculomotor plasticity (Dl) remains important and needs to be pursued actively. Again, although no NEI grants were funded in this category in FY 1984, there is intramural NEI research being performed on this subject.

Program Base categories Bl and B2 are closely related and should be combined. A reanalysis of the FY 1984 grants in each subprogram resulted in the addition of 2 grants from the Visual Processing and Amblyopia: Structure and Function: Cell and Systems subprogram, 1 grant from the Ocular Motility and Strabismus, Normal and Abnormal Development subprogram, and 1 grant from the Muscle Structure and Physiology subprogram for a net gain of 4 grants. Thus, 36 rather than 34 grants were funded in this subprogram in FY 1984.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: STRUCTURE AND FUNCTION, CONJUGATE EYE MOVEMENTS (5-J4)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM BASE								
1. Study the anatomy and operation of mesencephalic and pontine circuits involved in conjugate eye movements. (B1)	16	17	12	13 [1]	13	14	7	50.0
2. Study the circuits through which the cerebellum influences eye movements. (B2)	2	3	4	5	4	3	3	100.0
3. Identify and characterize all oculomotor subsystems and their interactions. (B3)	9	9	9	10	5	14	5	35.7
4. Study the role of higher brain centers in creating eye movements. (B4)	8	8	9	10	7	12	4	33.3
TOTAL FOR PROGRAM BASE	35	37	34 [0]	38 [1]	29 [0]	43	19	44.2
PROGRAM DEVELOPMENT PRIORITIES								
1. Discover and characterize all types of sensorimotor plasticity in the oculomotor system: Neural mechanisms and role of cerebellum. (D1)	2	3	0	0	0	1	0	
2. Develop hypotheses to explain eye movement disorders: Relate hypothetical system or model to clinical problems. (D2)	2	3	1	2	3	1	1	100.0
3. Study the influence of drugs on neurotransmitters in oculomotor subsystems. (D3)	0	2	0	0	0	2	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	4	8	1 [0]	2 [0]	3 [0]	4	1	25.0
TOTAL FOR SUBPROGRAM	39	45	35 [0]	40 [1]	32 [0]	47	20	42.6
(% OF PROGRAM)	(14.5)	(12.7)	(14.3)	(15.5)	(12.0)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: STRUCTURE AND FUNCTION, CONJUGATE EYE MOVEMENTS (5-J4)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Study the anatomy and operation of mesencephalic, pontine, and cerebellar circuits involved in conjugate eye movements. (B1)	EXPANDED (INCLUDES OLD B1, B2)	17	19	0	16	15
2. Identify and characterize oculomotor subsystems and their interactions. (B2)	SAME	9	7	0	10	10
3. Study the role of higher brain centers in creating eye movements. (B3)	SAME	8	9	0	10	8
TOTAL FOR PROGRAM BASE		34 [0]	35	0	36 [0]	33 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Discover and characterize types of sensorimotor plasticity in the oculomotor system. (D1)	LESS SPECIFIC	1	3	0	2	2 [1]
2. Identify, characterize, and define the functions of neurotransmitters, peptides, and other chemicals important in oculomotor subsystems. (D2)	EXPANDED (WAS D3)	1	3	0	0	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		2 [0]	6	0	2 [0]	3 [1]
TOTAL FOR SUBPROGRAM		36 [0]	41	0	38 [0]	36 [1]
(% OF PROGRAM)		(13.5)	(11.7)	(0.0)	(14.3)	(13.5)

Structure and Function: Vergence and Accommodation

11

Perspective on Recent Research

Research in this subprogram concerns behavioral studies of accommodation and vergence in human and primate infants and adults. Accurate accommodation is essential for bringing a clear image of the world onto the fovea, and accurate convergence is essential for clear binocular vision. Errors in either of these control loops, which in most circumstances are strongly interconnected, can destroy clear vision.

Progress in Areas Discussed in The 1983-1987 Plan

Both accommodation and vergence have been active areas of research in infant and adult humans. It has been shown in infants that vergence and accommodation are uncoupled in the absence of patterned stimuli.[1] In adults it has been found that dark focus and tonic vergence are differentially affected by near work, implying that they are determined by separate mechanisms.[2]

Recent neurophysiological work on juvenile rhesus monkeys has shown that neurons near the oculomotor nucleus code their frequency of discharge with respect to angle of vergence and that these neurons are insensitive to conjugate eye movements.[3] These results support the view that conjugate and vergence signals are generated independently and are combined at the extraocular motoneurons.

Accommodative range has also been studied in normal and amblyopic monkeys. Scientists have found using behavioral measurements in the rhesus monkey[4] that their accommodative range is somewhat larger than that of the human (17-18 D as opposed to 12 D in young humans). In strabismic or atropinized pigtailed macaque monkeys, loss of accommodation paralleled loss in contrast sensitivity. Deficits in accommodative range were found to be similar to those that accompany amblyopia in humans.[5]

New and Developing Areas of Research

Modern photographic and video techniques afford the possibility of registering both eye position (by corneal reflex) and degree of defocus by photorefraction in both eyes simultaneously.[6] Using photo-retinoscopy this can be accomplished with a single instrument.[7,8] These techniques thus afford the possibility of studying normal and pathological development of accommodation and convergence in unrestrained human infants and primates. The Panel believes that there is both a need and an opportunity for more research in this area and has recommended a substantial percentage increase in the number of grants.

Balance of Effort Within Subprogram

There has been no significant change in the total number of funded grants over the past few years. No new grants in developing areas have been funded.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The Panel believes study of the innervation of the ciliary muscle (Bl) is too specific an area of research to constitute a separate classification. As for the Program Development Priorities, the Panel believes that fundamental studies of the development and function of the accommodative and vergence systems continue to be crucial to an understanding of the genesis of strabismus and amblyopia. However, the current classification of this subprogram is too detailed and specific, given the small amount of projects it includes.

Recommended Changes in Program Base and/or Program Development Priorities

The Panel found Priorities Dl, D2, and D3 too specific and grouped them into a new Dl. Category D5, now D2, was expanded to include pupillary systems, which would include studies previously classified under Bl, which is deleted. As a result of this reclassification, one FY 1984 grant was transferred to the Muscle Structure and Physiology subprogram. Thus, 5, rather than 6 grants, were funded in this subprogram in FY 1984.

The Panel recommended an increase in funding in this subprogram because of the crucial importance of a thorough knowledge of accommodative and convergence feedback loops for the genesis of strabismus and amblyopia. The Panel believes that there are many people, particularly those in the ophthalmological and optometric professions who are qualified to conduct research in this area. The likelihood of the current funding increasing significantly depends largely upon the proper advertisement of these scientific opportunities.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: STRUCTURE AND FUNCTION, VERGENCE AND ACCOMMODATION (5-J5)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Study the innervation of ciliary muscle. (B1)	0	1	0	0	1	1	1	100.0
TOTAL FOR PROGRAM BASE	0	1	0 [0]	0 [0]	1 [0]	1	1	100.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Define accomodative/vergence stimuli for the neonate; characterize developing associated motor responses. (D1)	1	2	1 [1]	1	0	2	0	
2 Elucidate the accommodative/vergence relationships and the critical period for influencing them in the neonate. (D2)	0	2	0	0	1	1	1	100.0
3. Explore and define interactions/plasticity of vergence/accommodation in neonates: Normal and those with predilection for strabismus. (D3)	1	2	1	1	0	0	0	
4. Explain plasticity of anomalous retinal correspondence with some vergence movements and rigidity of normal correspondence in strabismics and nonstrabismics. (D4)	1	2	1	1	0	3	0	
5. Study the anatomy, physiology, and behavior in vergence and accommodation systems in animal models. (D5)	3	4	5	6	4	6	2	33.3
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	6	12	8 [1]	9 [0]	5 [0]	12	3	25.0
TOTAL FOR SUBPROGRAM	6	13	8 [1]	9 [0]	6 [0]	13	4	30.8
(% OF PROGRAM)	(2.2)	(3.7)	(3.2)	(3.5)	(2.2)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: STRUCTURE AND FUNCTION, VERGENCE AND ACCOMMODATION (5-J5)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM DEVELOPMENT PRIORITIES						
1. Elucidate the normal development of accommodation and convergence in human and nonhuman primate infants. (D1)	LESS SPECIFIC (COMBINES OLD D1, D2, D3)	0	4	0	0	0
2. Study the anatomy, physiology, and behavior in vergence accommodation, and pupillary systems in animal models. (D2)	EXPANDED (WAS D5)	3	6	0	2	1
3. Study normal and abnormal adult human vergence and accommodation. (D3)	LESS SPECIFIC (WAS D4)	2	4	0	3 [1]	5
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		5 [0]	14	0	5 [1]	6 [0]
TOTAL FOR SUBPROGRAM		5 [0]	14	0	5 [1]	6 [0]
(% OF PROGRAM)		(1.9)	(4.0)	(0.0)	(1.9)	(2.2)

Structure and Function: Muscle Structure and Physiology

12

Balance of Effort Within Subprogram

The Panel chose not to conduct a detailed review of this subprogram but noted that the Plan's recommended increase in one of the two Program Development Priorities was met and exceeded in FY 1984, bringing about the desired FY 1983 level in the overall subprogram.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The two Program Development Priorities continue to remain relevant. A new area of emphasis should be backing up the new clinical application of neurotoxins, described in the next chapter, with laboratory studies of their short- and long-term affects on extraocular muscles.

Recommended Changes in Program Base and/or Program Development Priorities

The two Program Development Priorities should be combined, and having achieved their combined funding targets, be classified as the new Program Base. A new Program Development Priority should be added on laboratory studies of the affect of neurotoxins on extraocular muscle. As a result of the restructuring of this subprogram one FY 1984 grant was transferred out to the Conjugate Eye Movements subprogram and one was added from the Vergence and Accommodation subprogram. One Small Grant was transferred from the Strabismus subprogram.

UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: STRUCTURE AND FUNCTION, MUSCLE STRUCTURE AND PHYSIOLOGY (5-J6)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1. Determine the molecular and cellular properties of extraocular muscles and the organization and function in normal and pathological conditions. (D1)	3	4	3	3	5	4	2	50.0
2. Study the properties of other muscles or muscle systems that directly affect the visual process. (D2)	1	2	1	1	1	5	1	20.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	4	6	4 [0]	4 [0]	6 [0]	9	3	33.3
TOTAL FOR SUBPROGRAM	4	6	4 [0]	4 [0]	6 [0]	9	3	33.3
(% OF PROGRAM)	(1.5)	(1.7)	(1.6)	(1.5)	(2.2)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: STRUCTURE AND FUNCTION, MUSCLE STRUCTURE AND PHYSIOLOGY (5-J6)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Determine the molecular, physiological, and anatomical properties of extraocular muscles and other muscle systems that directly affect the visual process. (B1)	MOVED, EXPANDED (INCLUDES OLD D1, D2)	5	6	0	3	7 [1]
TOTAL FOR PROGRAM BASE		5 [0]	6	0	3 [0]	7 [1]
PROGRAM DEVELOPMENT PRIORITIES						
1. Study the long- and short-term effects of neurotoxins on extraocular muscles. (D1)	NEW	1 [1]	2	0	0 [1]	0 [1]
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		1 [1]	2	0	0 [1]	0 [1]
TOTAL FOR SUBPROGRAM		6 [1]	8	0	3 [1]	7 [2]
(% OF PROGRAM)		(2.2)	(2.3)	(0.0)	(1.1)	(2.6)

Disorders: Strabismus

13

Perspective on Recent Research

The treatment of disorders of ocular motility under the subheading of strabismus has undergone a recent renaissance with the application of Oculinum (botulinum toxin) and the expansion of its role in strabismus therapy. In addition, a new multicenter trial of the use of prisms in predicting surgical amounts is now under way. There are ongoing needs and opportunities in the field of strabismus, such as studying the predictability of surgical therapy, the duration of the results and the factors which influence reoperative rates. New pharmacological agents of longer duration and new vehicles which permit the sustained release of pharmacological agents are also areas that merit research attention.

Progress in Areas Discussed in The 1983-1987 Plan

Following publication of the Plan, which recommends the support of a multicenter trial of the use of prism therapy in the treatment of esotropia, members of the vision research community with an active interest in strabismus initiated such a study.[1] This trial, involving eleven clinical centers and a data coordinating center, represents a landmark effort on the part of the strabismus research community to achieve among its members a commonality of goals and methodologies to best pursue them.

Perhaps no subprogram within the Plan so needed increased emphasis as did strabismus research. Still another area, hinted at in the Plan but now more fully developed, has been the development, investigation, and use of botulinum toxin in the treatment of strabismus and blepharospasm.[2,3] This drug is one of the recent research advances that promises a positive impact on patient care when its testing stages are over.

New and Developing Areas of Research

As discussed above, the Panel believes that the recent resurgence of interest in applied research in the field of strabismus represents a significant advance over the modest beginnings of research efforts envisioned in the Plan.

Balance of Effort Within Subprogram

After an initial lag during which few applications for strabismus research projects were submitted for consideration, the total number of projects recommended was actually achieved in FY 1984 because of the funding of a multicenter trial of prism therapy in strabismus. This, however, may give a false sense of satisfaction about the research effort in regard to this entire subprogram. Strabismus is an area that does need research attention in the form of well-designed individual research grants as well as clinical trials of particular forms of therapy. In categories other than DI, the objectives recommended by the Plan were not met. Steps need to be taken to organize the strabismus community's effort to conceive, plan, and execute individual research grants.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

Since the publication of the Plan in 1983, strabismus research has shown appreciable growth due primarily to the application—long overdue—of the discipline of clinical trial-based research to the field and the introduction of a new concept, botulinum toxin, in the treatment of strabismus. There is a real need for several clinical trials of botulinum toxin, such as for the treatment of congenital estropia[4] and other forms of strabismus as well. The Panel believes that three of the Plan's Program Development Priorities, D3, D4, and D6 are either taken care of in other categories or not likely soon to produce new research grant applications.

Recommended Changes in Program Base and/or Program Development Priorities

Within the context of the above, the Evaluation Panel recommends streamlining and updating the Program Development Priorities to reflect areas where productive research can be anticipated within the next few years. The Panel believes that the widespread use of Oculinum merited its move to Program Development Priorities. Categories D3, D4, and D6 were either taken care of in other categories or not likely to be productive of research applications at this time. To this end, the Panel recommends that the FY 1984 level of 10 regular research grants and 13 projects supporting clinical trials of nonpharmacological treatments of strabismus be increased to 13 regular research grants plus 18 grants to support additional multicenter clinical trials, particularly of pharmacological treatments of strabismus. This will, by no means, exhaust the field of strabismus research but perhaps serve to fire the imagination of young researchers coming into the field. The one Small

Grant previously classified in this subprogram was moved to the Muscle Structure and Physiology subprogram.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: DISORDERS, STRABISMUS (5-J8)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
	[No. R03, R43, R44 in brackets]							
PROGRAM BASE								
1. Study the sensory/perceptual consequences of strabismus. (B1)	3	3	2	1	2	5	2	40.0
TOTAL FOR PROGRAM BASE	3	3	2 [0]	1 [0]	2 [0]	5	2	40.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Conduct clinical investigations of surgical treatments for strabismus. (D1)	2	3	2	2	15	16	15	93.8
2. Study pharmacological and other treatments of strabismus. (D2)	2	5	2	2	2 [1]	5	3	60.0
3. Investigate the importance of sensory stimulation or changing the angle of strabismus. (D3)	0	2	0	0	0	1	0	
4. Study the importance of chronology of treatment for outcome. (D4)	0	2	0	1	1	1	1	100.0
5. Continue genetic/epidemiologic studies of risk factors for strabismus. (D5)	1	2	1	1	0	3	0	
6. Develop better quantitative eye movement recording techniques to diagnose strabismus. (D6)	0	1	0	0	1	3	1	33.3
7. Develop animal models of strabismus. (D7)	1	6	3	3	2	2	0	
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	6	21	8 [0]	9 [0]	21 [1]	31	20	64.5
TOTAL FOR SUBPROGRAM	9	24	10 [0]	10 [0]	23 [1]	36	22	61.1
(% OF PROGRAM)	(3.3)	(6.7)	(4.1)	(3.8)	(8.6)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: DISORDERS, STRABISMUS (5-J8)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM BASE						
1. Study the sensory/perceptual consequences of strabismus. (B1)	SAME	3	4	0	4	5
2. Conduct clinical investigations of nonpharmacological treatments for strabismus. (B2)	MOVED (WAS D1)	16	3	13	16	16
TOTAL FOR PROGRAM BASE		19 [0]	7	13	20 [0]	21 [0]
PROGRAM DEVELOPMENT PRIORITIES						
1. Study pharmacological treatments of strabismus. (D1)	MOVED (WAS D2)	1	0	5	1	2
2. Conduct genetic and epidemiologic studies of risk factors for strabismus. (D2)	MOVED (WAS D5)	0	1	0	0	1
3. Use animal models of strabismus to study vergence behavior in this disorder and the underlying anatomy and physiology of the vergence system. (D3)	MORE SPECIFIC (WAS D7) [DELETED OLD D3, D4, D6]	3	5	0	5	4
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		4 [0]	6	5	6 [0]	7 [0]
TOTAL FOR SUBPROGRAM		23 [0]	13	18	26 [0]	28 [0]
(% OF PROGRAM)		(8.6)	(3.7)	(64.3)	(9.8)	(10.5)

Disorders: Motor Neuro-Ophthalmic Disorders

14

Perspective on Recent Research

The application of findings from basic science research, new control systems, analytical techniques, and technical advances in recording eye movements have provided a milieu in which important progress can be made in understanding human oculomotor disorders. This is reflected in the increasing number of research grants being funded in this area and also the recommended shift of emphasis from the Program Base to Program Development Priorities.

Progress in Areas Discussed in The 1983-1987 Plan

One of the most important advances in the area of motor neuro-ophthalmic research has been the application of the search coil technique for measuring eye movements in the clinical setting. The technique allows sensitive and accurate recordings of eye movements in the horizontal and vertical planes and this is reflected in the increased number of publications in which ocular motor function is precisely measured and quantified. Also, control systems analysis is now becoming the standard, rather than the exception, in analyzing ocular motor disorders.[1]

Likewise, another important area of research progress which has important applications to motor neuro-ophthalmology is the study of adaptive mechanisms in ocular motor control.

There is a large number of patients with unexplained neuro-ophthalmic symptomatology that relates to vestibular system dysfunction. These patients need to be studied quantitatively with measurements of the vestibulo-ocular reflex including both semicircular canal-mediated and otolith-mediated functions. In particular, the vertical and torsional as well as the horizontal vestibulo-ocular reflex can be assessed quantitatively by rotating the head in the appropriate plane and recording eye movements using the search coil technique. Likewise, new tests of otolith function (off axis-rotation, "dumping" of post rotary nystagmus by changes in head position) can be applied to neuro-ophthalmic patients.

New and Developing Areas of Research

With the advent of a practical search coil to measure torsional eye movements, it has become possible to study the torsional system in neuro-ophthalmic patients.[2] This technique is waiting to be applied to patients with a variety of oculomotor disorders.

There is a large number of patients with unexplained neuro-ophthalmic symptomatology that relates to vestibular system dysfunction. These patients need to be studied quantitatively with measurements of the vestibulo-ocular reflex, including both semicircular canal-mediated and otolith-mediated functions. In particular, the vertical and torsional as well as the horizontal vestibulo-ocular reflex can be assessed quantitatively by rotating the head in the appropriate plane and recording eye movements using the search coil technique. Likewise, new tests of otolith function (off axis rotation, "dumping" of post rotary nystagmus by changes in head position) can be applied to neuro-ophthalmic patients.[3]

Balance of Effort Within Subprogram

Funding in motor neuro-ophthalmic disorders significantly improved by FY 1984 over the 1981 base period, although it did not quite reach the Plan's recommendations for 1983. This pattern of funding reflects the potential of this area for productive research.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

The Evaluation Panel believes that the research in this subprogram categorized as the Program Base should now be designated as a Program Development Priority because manpower and techniques for important progress in this area are now available. The Panel also believes that Program Development Priorities D2 and D3 are too specific and should be eliminated. Work in those areas could be classified under a more general heading.

Study of lid movements in neurological disease should be emphasized as well as eye movements because of the strong ophthalmic interest in treatment of disorders of eye lid function and blinking. It is also thought pertinent to encourage studies of adaptation and their clinical applications because this area is important to both the diagnosis and management of patients with neuro-ophthalmic disorders.

Recommended Changes in Program Base and/or Program Development Priorities

In response to the above, the Panel decided to both consolidate and expand the Plan's recommendations and to increase the number of projects recommended by six over the nine the Plan recommends for FY 1983 to a total of 15. Three grants previously classified under the subprogram Conjugate Eye Movements, specifically in Program Development Priority D2 which calls for the development of hypotheses to explain eye movement disorders, should also be transferred to this subprogram.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: DISORDERS, MOTOR NEURO-OPHTHALMIC DISORDERS (5-J9)

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84 Received	Funded	Percent
			[No. R03, R43, R44 in brackets]					
PROGRAM BASE								
1. Study the cellular aspects and system modeling of neuro-ophthalmic diseases. (B1)	2	2	1	1	2	4	1	25.0
TOTAL FOR PROGRAM BASE	2	2	1 [0]	1 [0]	2 [0]	4	1	25.0
PROGRAM DEVELOPMENT PRIORITIES								
1. Study of eye movements in neurological diseases. (D1)	2	4	3	5	5	8	4	50.0
2. Compare computer analysis of oculomotor functions with clinical analysis by a trained neuro-ophthalmologist. (D2)	0	1	0	0	0	0	0	
3. Develop new technology for automated eye movement-recording systems. (D3)	0	2	0	0	0 [1]	3	1	33.3
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	2	7	3 [0]	5 [0]	5 [1]	11	5	45.5
TOTAL FOR SUBPROGRAM	4	9	4 [0]	6 [0]	7 [1]	15	6	40.0
(% OF PROGRAM)	(1.5)	(2.5)	(1.6)	(2.3)	(2.6)			

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OCULAR MOTILITY AND STRABISMUS: DISORDERS, MOTOR NEURO-OPHTHALMIC DISORDERS (5-J9)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation Research Grants	Update Panel Recommendation Clinical Trials	Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
PROGRAM DEVELOPMENT PRIORITIES						
1. Study eye and lid movements in neurological diseases. (D1)	EXPANDED	5	9	0	5 [1]	4 [1]
2. Determine the basis of clinically important eye movement disorders; relate laboratory studies or models to clinical problems of diagnosis and adaptation. (D2)	LESS SPECIFIC (INCLUDES OLD B1, D2, D3)	2 [1]	6	0	2 [1]	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		7 [1]	15	0	7 [2]	5 [1]
TOTAL FOR SUBPROGRAM		7 [1]	15	0	7 [2]	5 [1]
(% OF PROGRAM)		(2.6)	(4.3)	(0.0)	(2.6)	(1.9)

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OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA

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Optics and Refractive Errors, Including Myopia

15

Perspective on Recent Research

Most of the work in this area has concentrated on the study of refractive errors using animal models and on the development of mass screening methods for refractive errors.

The Plan emphasizes a broad approach to the problems of myopia, including biomechanical studies of the eye, studies of the influence of refractive state on the growth of the eye, studies of presbyopia, and the development of new refractive screening methods. The Panel envisioned that work would proceed both on humans directly and, where appropriate, on animal models. We continue to believe that work on this broad front is important and have reaffirmed the original priorities with only slight modification.

Progress in Areas Discussed in The 1983-1987 Plan

Animal models of myopia. Tree shrews and chicks develop substantial myopia in response to suturing closed the lid of an eye. In the tree shrew this myopia persists in spite of a flattening of the cornea in the closed eye.[1] In the chick it has been found that the myopia is reversible, and that its cause and remission is directly related to rates of growth in the axial length of the eye.[2]

Mass screening for refractive errors. To screen for refractive errors in infants and young children it is necessary to have some idea of the distribution of normal refractions. A number of studies using different methods have confirmed the existence of against-the-rule myopia in populations of infants in the United States and have charted its diminution with age.[3-5] This astigmatism of infancy is also known to be corneal in origin.[6] Recently, it has been shown that population samples of Chinese infants show with-the-rule myopia, indicating that genetic background of the infant may be important in determining whether or not it is ametropic.[7]

New and Developing Areas of Research

Considerable progress has been made in photorefractive techniques, especially photoretinoscopy (Kaakinen, Norcia and Day, Howland). Photoretinoscopy is a particularly appealing screening technique in that an in-focus view of the subject is obtained which shows in a single picture the corneal reflexes and the retinoscopic reflexes of both eyes simultaneously. Moreover, the optical basis of the technique has now been explicated (Howland, Braddick, and Bobier). With the advent of computer framegrabbers, which together with a video camera can capture photorefractive pictures instantaneously, it is to be anticipated that photorefractive screening will be more and more widely used.

Balance of Effort Within Subprogram

There has been some lag in the response to calls for epidemiological studies of the risk factors in myopia and for clinical trials of the treatment of myopia. The cause of this lag is unknown.

Adequacy and Current Relevance of The Program Base and Program Development Priorities

All of the categories of research in this subprogram have been designated Program Development Priorities. The Panel believes that epidemiological studies of risk factors for myopia, clinical trials of treatments of myopia, and research on the influence of refractive and accommodative states on the development of the eye should be emphasized more in the Priorities.

Recommended Changes in Program Base and/or Program Development Priorities

Minor changes have been made in the Program Development Priorities. The first Priority has been divided into two new Priorities, animal (Dl) and human (D3) studies. The original Priority D3, referring to the development of special purpose refracting instruments, has been subsumed under D4.

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UPDATED NATIONAL PLAN SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA (5-K1)

[No. R03, R43, R44 in brackets]

	Projects FY 1981	Panel Rec. FY 1983	Projects FY 1982	Projects FY 1983	Projects FY 1984	Applications FY 1983-84		
						Received	Funded	Percent
PROGRAM DEVELOPMENT PRIORITIES								
1. Study myopia using animal models and physiochemical approaches. (D1)	3	7	3 [1]	4 [1]	4	2	2	100.0
2. Conduct epidemiological studies of risk factors for myopia and clinical trials of treatments for myopia. (D2)	0	2	0	0	0 [1]	3	1	33.3
3. Develop/test special purpose refracting instrument. (D3)	0	2	0	0	0	0	0	
4. Develop mass screening methods for refractive errors. (D4)	0	1	1	1	1	2	2	100.0
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES	3	12	4 [1]	5 [1]	5 [1]	7	5	71.4
ADDITIONAL RESEARCH CATEGORIES (FY 1982 AND LATER)								
1. Additional Research Categories. (A1)	0	0	0 [1]	0	0	1	0	
TOTAL FOR ADDITIONAL RESEARCH CATEGORIES	0	0	0 [1]	0 [0]	0 [0]	1	0	0.0
TOTAL FOR SUBPROGRAM	3	12	4 [2]	5 [1]	5 [1]	8	5	62.5
(% OF PROGRAM)	(1.1)	(3.4)	(1.6)	(1.9)	(1.9)			
TOTAL FOR PROGRAM	268	353	244 [12]	257 [8]	266 [11]	448	174	38.8

REVISED SUBPROGRAM RESOURCE TABLE

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING

OPTICS AND REFRACTIVE ERRORS, INCLUDING MYOPIA (5-K1)

	Changes from 1983-87 Plan	Projects FY 1984 [No. R03, R43, R44]	Update Panel Recommendation		Projects FY 1985 [No. R03, R43, R44]	Projects FY 1986 [No. R03, R43, R44]
			Research Grants	Clinical Trials		
PROGRAM DEVELOPMENT PRIORITIES						
1. Study refractive errors using animal models. (D1)	LESS SPECIFIC	4	8	0	5	4
2. Conduct epidemiological studies of risk factors for myopia and clinical trials of treatments for myopia. (D2)	SAME	0 [1]	2	0	0	0
3. Study the influence of refractive and accommodative states on the development of the human eye. (D3)	MORE SPECIFIC	0	2	0	0	1
4. Develop mass screening methods for refractive errors. (D4)	SAME	1	2	0	1	1
TOTAL FOR PROGRAM DEVELOPMENT PRIORITIES		5 [1]	14	0	6 [0]	6 [0]
TOTAL FOR SUBPROGRAM		5 [1]	14	0	6 [0]	6 [0]
(% OF PROGRAM)		(1.9)	(4.0)	(0.0)	(2.3)	(2.2)
TOTAL FOR PROGRAM		267 [11]	351	28	265 [11]	267 [5]

*U.S. G.P.O. 1987-201-778:61161

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